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(54) **CYCLIC GUANIDINES, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF USE**

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(57) **ABSTRACT**

The present invention relates to cyclic guanidines, compositions containing such compounds and methods of treatment. The compounds are glucagon receptor antagonists and thus are useful for treating, preventing or delaying the onset of type 2 diabetes mellitus.

CYCLIC GUANIDINES, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF USE

BACKGROUND OF THE INVENTION

[0001] The present invention relates to cyclic guanidine derivatives, compositions containing such compounds and methods of treating type 2 diabetes mellitus.

[0002] Diabetes refers to a disease process derived from multiple causative factors and is characterized by elevated levels of plasma glucose (hyperglycemia) in the fasting state or following glucose administration during an oral glucose tolerance test. Frank diabetes mellitus (e.g., a blood glucose level≧126 mg/dL in a fasting state) is associated with increased and premature cardiovascular morbidity and mortality, and is related directly and indirectly to various metabolic conditions, including alterations of lipid, lipoprotein and apolipoprotein metabolism.

[0003] Patients with non-insulin dependent diabetes mellitus (type 2 diabetes mellitus), approximately 95% of patients with diabetes mellitus, frequently display elevated levels of serum lipids, such as cholesterol and triglycerides, and have poor blood-lipid profiles, with high levels of LDL-cholesterol and low levels of HDL-cholesterol. Those suffering from Type 2 diabetes mellitus are thus at an increased risk of developing macrovascular and microvascular complications, including coronary heart disease, stroke, peripheral vascular disease, hypertension (for example, blood pressure≧130/80 mmHg in a resting state), nephropathy, neuropathy and retinopathy.

[0004] Patients having type 2 diabetes mellitus characteristically exhibit elevated plasma insulin levels compared with nondiabetic patients; these patients have developed a resistance to insulin stimulation of glucose and lipid metabolism in the main insulin-sensitive tissues (muscle, liver and adipose tissues). Thus, Type 2 diabetes, at least early in the natural progression of the disease is characterized primarily by insulin resistance rather than by a decrease in insulin production, resulting in insufficient uptake, oxidation and storage of glucose in muscle, inadequate repression of lipolysis in adipose tissue, and excess glucose production and secretion by the liver. The net effect of decreased sensitivity to insulin is high levels of insulin circulating in the blood without appropriate reduction in plasma glucose (hyperglycemia). Hyperinsulinemia is a risk factor for developing hypertension and may also contribute to vascular disease.

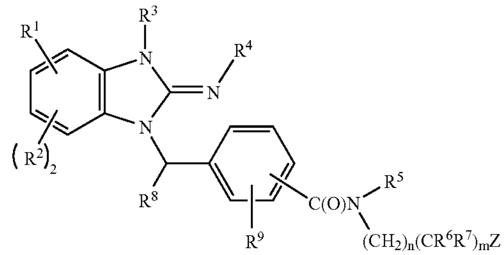
[0005] Glucagon serves as the major regulatory hormone attenuating the effect of insulin in its inhibition of liver gluconeogenesis and is normally secreted by α-cells in pancreatic islets in response to falling blood glucose levels. The hormone binds to specific receptors in liver cells that triggers glycogenolysis and an increase in gluconeogenesis through cAMP-mediated events. These responses generate glucose (e.g. hepatic glucose production) to help maintain euglycemia by preventing blood glucose levels from falling significantly.

[0006] In addition to elevated levels of circulating insulin, type II diabetics have elevated levels of plasma glucagon and increased rates of hepatic glucose production. Antagonists of glucagon are useful in improving insulin responsiveness in the liver, decreasing the rate of gluconeogenesis and lowering the rate of hepatic glucose output resulting in a decrease in the levels of plasma glucose.

SUMMARY OF THE INVENTION

[0007] The present invention is directed to a compound represented by formula I:

I



or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0008] R^1 represents H or is independently selected from the group consisting of:

[0009] a) OH, halo, CO_2R^a, $C(O)NR^bR^c$, NR^bR^c, CN or $S(O)_pR^d$;

[0010] b) C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, OC_{1-10}alkyl, OC_{3-10}alkenyl and OC_{3-10}alkynyl, said groups being optionally substituted with:

[0011] (1) 1-5 halo groups up to a perhaloalkyl group;

[0012] (2) 1 oxo group;

[0013] (3) 1-2 OH groups;

[0014] (4) 1-2 C_{1-10}alkoxy groups, each optionally substituted with: up to five halo or a perhaloalkoxy, 1 OH or CO_2R^a group;

[0015] (5) 1 CO_2R^a or $S(O)_pR^d$;

[0016] (6) 1-2 Aryl, Hetcy or HAR groups, each optionally substituted as follows:

[0017] (a) 1-5 halo groups,

[0018] (b) 1 OH, CO_2R^a, CN, $S(O)_pR^d$, NO_2 or $C(O)NR^bR^c$,

[0019] (c) 1-2 C_{1-10}alkyl or alkoxy groups, each optionally substituted with: 1-5 halo, up to perhaloalkyl, and 1-2 OH or CO_2R^a groups; and

[0020] (d) 1-2 phenyl rings, each of which is optionally substituted as follows: 1-5 halo groups up to perhalo, 1-3 C_{1-10}alkyl or alkoxy groups, each being further optionally substituted with 1-5 halo up to perhalo, or 1-2 hydroxy or CO_2R^a groups;

[0021] c) Aryl, HAR, Hetcy, —O-Aryl, —O-HAR and —O-Hetcy, each optionally substituted as set forth below:

[0022] (1) 1-3 C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl groups optionally substituted with 1-5 halo groups; 1-2 OH groups; phenyl optionally substituted with 1-3 halo, C_{1-6}alkyl or C_{1-6} alkoxy groups, the alkyl and alkoxy groups being further optionally substituted with 1-3 halo groups; CO_2R^a; CN or $S(O)_pR^d$ groups; and

[0023] (2) 1-3 C_{1-10}alkoxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups, 1-2 OH; phenyl optionally substituted with 1-3 halo, C_{1-6}alkyl or C_{1-6} alkoxy groups, the alkyl and alkoxy groups being further optionally substituted with 1-3 halo groups;

[0024] CO_2R^a; CN or $S(O)_pR^d$ groups; said Aryl, HAR, Hetcy —O-Aryl, —O-HAR and —O-Hetcy group c) being further optionally substituted on carbon by a group selected from the group consisting of;

[0025] (3) 1-5 halo groups;

[0026] (4) 1-2 OH groups;

[0027] (5) 1 $S(O)_pR^d$, NO_2 or CN group;

[0028] (6) 1-2 CO_2R^a;

[0029] (7) —$C(O)NR^bR^c$;

each R^2represents H or is independently selected from the group consisting of:

[0030] a) OH, halo, CO_2R^a, $C(O)NR^bR^c$, NR^bR^c, CN or $S(O)_pR^d$;

[0031] b) C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, OC_{1-10}alkyl, OC_{3-10}alkenyl and OC_{3-10}alkynyl, said groups being optionally substituted with:

[0032] (1) 1-5 halo groups up to a perhaloalkyl group;

[0033] (2) 1 oxo group;

[0034] (3) 1 OH group;

[0035] (4) 1 C_{1-10}alkoxy group, each optionally substituted with: up to five halo or a perh loalknxy, 1 OH or CO_2R^a group;

[0036] (5) 1 CO_2R^a or $S(O)_pR^d$;

[0037] (6) 1 Aryl, Hetcy or HAR group, each optionally substituted as follows:

[0038] (a) 1-5 halo groups,

[0039] (b) 1 OH, CO_2R^a, CN, $S(O)_pR^d$, NO_2 or $C(O)NR^bR^c$,

[0040] (c) 1-2 C_{1-10}alkyl or alkoxy groups, each optionally substituted with: 1-5 halo, up to perhaloalkyl, and 1-2 OH or CO_2R^a groups; and

[0041] (d) 1-2 phenyl rings, each of which is optionally substituted as follows: 1-5 halo groups up to perhalo; 1-3 C_{1-10}alkyl or alkoxy groups, each being further optionally substituted with 1-5 halo up to perhalo; and 1-2 hydroxy or CO_2R^a groups;

[0042] c) Aryl, HAR, Hetcy, —O-Aryl, —O-HAR and —O-Hetcy, each optionally substituted as set forth below:

[0043] (1) 1-3 C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl groups optionally substituted with 1-5 halo groups, 1-2 OH, phenyl, CO_2R^a, CN or $S(O)_pR^d$ groups;

[0044] (2) 1-3 C_{1-10}alkoxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups, 1-2 OH, phenyl, CO_2R^a, CN or $S(O)_pR^d$ groups;

said Aryl, HAR or Hetcy group c) being further optionally substituted on carbon by a group selected from the group consisting of;

[0045] (3) 1-5 halo groups up to perhalo;

[0046] (4) 1 OH group;

[0047] (5) 1 $S(O)_pR^d$, NO_2 or CN group;

[0048] (6) 1 CO_2R^a;

[0049] R^3 is selected from the group consisting of:

[0050] a) C_{1-10}alkyl or C_{2-10}alkenyl, each optionally substituted with

[0051] 1-5 halo groups up to perhalo;

[0052] 1-2 OH, C_{1-3}alkoxy or haloC_{1-3}alkoxy groups;

[0053] 1-2 NR^cR^d groups; and

[0054] 1-2 Aryl, HAR or Hetcy groups, each optionally substituted with 1-3 halo groups and 1-2 groups selected from CN, NO_2, C_{1-3}alkyl, haloC_{1-3}alkyl, C_{1-3}alkoxy and haloC_{1-3}alkoxy groups,

[0055] b) Aryl, HAR or Hetcy, each optionally substituted with 1-3 halo groups and 1-2 groups selected from CN, NO_2, C_{1-3}alkyl, haloC_{1-3}alkyl, C_{1-3}alkoxy and haloC_{1-3}alkoxy groups;

[0056] R^4 is independently selected from the group consisting of: Aryl, HAR or Hetcy, each optionally substituted as set forth below:

[0057] (1) 1-3 C_{1-14}alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl groups optionally substituted with 1-5 halo groups, 1-2 OH, CO_2R^a, CN or $S(O)_pR^d$ groups or phenyl optionally substituted as follows: 1-5 halo groups up to perhalo; 1-3 C_{1-10}alkyl or alkoxy groups, each being further optionally substituted with 1-5 halo up to perhalo, or 1-2 hydroxy or CO_2R^1 groups;

[0058] (2) 1-3 C_{1-10}alkoxy or C_{3-10}alkenyloxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups, 1-2 OH, CO_2R^a, CN, $S(O)_pR^d$, and phenyl optionally substituted as follows: 1-5 halo groups up to perhalo; 1-3 C_{1-10}alkyl or alkoxy groups, each being further optionally substituted with 1-5 halo up to perhalo, or 1-2 hydroxy or CO_2R^a groups;

[0059] (3) 1-2 Aryl, HAR or Hetcy, OAryl, OHAR or OHetcy groups, each optionally substituted as follows:

[0060] (i) 1-3 halo groups;

[0061] (ii) 1-2 C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl groups each optionally substituted with 1-5 halo groups, 1-2 OH, phenyl, CO_2R^a, CN or $S(O)_pR^d$ groups;

[0062] (iii) 1-2 C_{1-10}alkoxy groups the alkyl portion of which being optionally substituted with 1-5 halo groups, 1-2 OH, phenyl, CO_2R^a, CN or $S(O)_pR^d$ groups; and

[0063] (iv) 1-2 CO_2R^a, $S(O)_pR^d$, CN, NR^bR^c, NO_2 or OH groups;

said Aryl, HAR or Hetcy group R^4 being further optionally substituted on carbon by a group selected from the group consisting of;

[0064] (4) 1-5 halo groups;

[0065] (5) 1-2 OH groups;

[0066] (6) 1 $S(O)_pR^d$, NO_2 or CN group;

[0067] (7) 1-2 CO_2R^a;

[0068] R^5 represents H or C_{1-6}alkyl;

[0069] R^6 is selected from the group consisting of H, OH, F or C_{1-3}alkyl;

[0070] R^7 is H or F, or R^6 and R^7 are taken in combination and represent oxo;

[0071] R8 represents H or C_{1-6}alkyl, optionally substituted with OH and 1-5 halo groups up to perhalo;

[0072] R^9 represents H, halo, OH, C_{1-6}alkyl, optionally substituted with 1-5 halo groups up to perhalo, or C_{1-6}alkoxy, optionally substituted with 1-3 halo groups up to perhalo,

or when R^9 is ortho to the benzylic group, R^8 and R^9 can be taken together and represent a —$(CH_2)_{2-4}$— or a —O—$(CH_2)_{1-3}$— group;

[0073] R^a is H or C_{1-10}alkyl, optionally substituted with phenyl, OH, OC_{1-6}alkyl, CO_2H, CO_2C_{1-6}alkyl and 1-3 halo groups;

[0074] R^b is H or C_{1-10}alkyl;

[0075] R^c is H or is independently selected from:

[0076] (a) C_{1-10}alkyl, optionally substituted with OH, OC_{1-6}alkyl, CO_2H, CO_2C_{1-6}alkyl, and 1-3 halo groups;

[0077] (b) Aryl or Ar—C_{1-6}alkyl, each optionally substituted with 1-5 halos and 1-3 members selected from the group consisting of: CN, OH, C_{1-10}alkyl and OC_{1-10}alkyl, said alkyl and alkoxy being further optionally substituted with 1-5 halo groups up to perhalo;

[0078] (c) Hetcy or Hetcy-C_{1-6}alkyl, optionally substituted with 1-5 halo groups and 1-3 groups selected from: oxo, C_{1-10}alkyl and OC_{1-10}alkyl, said alkyl and alkoxy being further optionally substituted with 1-5 halo groups up to perhalo; and

[0079] (d) HAR or HAR-C_{1-6}alkyl, optionally substituted with 1-5 halo groups and 1-3 groups selected from: C_{1-10}alkyl and OC_{1-10}alkyl, said alkyl and alkoxy being further optionally substituted with 1-5 halo groups up to perhalo;

[0080] R^d is C_{1-10}alkyl, Aryl or Ar—C_{1-10}alkyl;

[0081] m is an integer selected from 0, 1 and 2;

[0082] n is an integer selected from 0 to 6;

[0083] p is an integer selected from 0, 1 and 2, and

[0084] when at least one of m and n is other than 0, Z is selected from CO_2R^a, 5-tetrazolyl and 5-(2-oxo-1,3,4-oxadiazolyl), and when both m and n are 0, Z is selected from 5-tetrazolyl and 5-(2-oxo-1,3,4-oxadiazolyl).

DETAILED DESCRIPTION OF THE INVENTION

[0085] The invention is described herein in detail using the terms defined below unless otherwise specified.

[0086] "Alkyl", as well as other groups having the prefix "alk", such as alkoxy, alkanoyl and the like, means carbon chains which may be linear, branched, or cyclic, or combinations thereof, containing the indicated number of carbon atoms. If no number is specified, 1-10 carbon atoms are intended for linear or branched alkyl groups. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl and the like. Cycloalkyl is a subset of alkyl; if no number of atoms is specified, 3-10 carbon atoms are intended, forming 1-3 carbocyclic rings that are fused. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, decahydronaphthyl and the like.

[0087] "Alkenyl" means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched or combinations thereof. Examples of alkenyl include vinyl, alkyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

[0088] "Alkynyl" means carbon chains which contain at least one carbon-carbon triple bond, and which may be linear or branched or combinations thereof. Examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like.

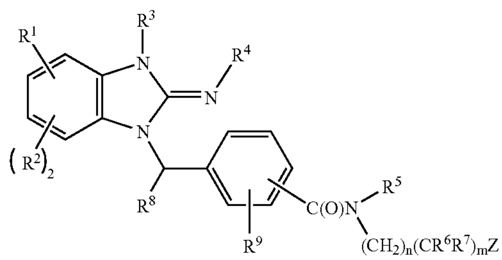
[0089] "Aryl" (Ar) means mono- and bicyclic aromatic rings containing 6-12 carbon atoms. Examples of aryl include phenyl, naphthyl, indenyl and the like. "Aryl" also includes monocyclic rings fused to an aryl group. Examples include tetrahydronaphthyl, indanyl and the like.

[0090] "Heteroaryl" (HAR) means a mono- or bicyclic aromatic ring or ring system containing at least one heteroatom selected from O, S and N, with each ring containing 5 to 6 atoms. Examples include pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl, thienyl, pyrimidyl, pyridazinyl, pyrazinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, furo(2,3-b)pyridyl, quinolyl, indolyl, isoquinolyl and the like. Heteroaryl also includes aromatic heterocyclic groups fused to heterocycles that are non-aromatic or partially aromatic, and aromatic heterocyclic groups fused to cycloalkyl rings. Heteroaryl also includes such groups in charged form, e.g., pyridinium.

[0091] "Heterocyclyl" (Hetcy) means mono- and bicyclic saturated rings and ring systems containing at least one heteroatom selected from N, S and O, each of said ring having from 3 to 10 atoms in which the point of attachment may be carbon or nitrogen. Examples of "heterocyclyl" include pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl, 2,3-dihydrofuro(2,3-b)pyridyl, benzoxazinyl, tetrahydrohydroquinolinyl, tetrahydroisoquinolinyl, dihydroindolyl, and the like. The term also includes partially unsaturated monocyclic rings that are not aromatic, such as 2- or 4-pyridones attached through the nitrogen or N-substituted-(1H,3H)-pyrimidine-2,4-diones (N-substituted uracils). Heterocyclyl-moreover includes such moieties in charged form, e.g., piperidinium.

[0092] "Halogen" (Halo) includes fluorine, chlorine, bromine and iodine.

[0093] In its broadest aspect, a compound represented by formula I: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or a pharmaceutically acceptable salt or solvate thereof is disclosed, wherein:

[0094] R^1 represents H or is independently selected from the group consisting of:

[0095] a) OH, halo, CO_2R^a, $C(O)NR^bR^c$, NR^bR^c, CN or $S(O)_pR^d$;

[0096] b) C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, OC_{1-10}alkyl, OC_{3-10}alkenyl and OC_{3-10}alkynyl, said groups being optionally substituted with:

[0097] (1) 1-5 halo groups up to a perhaloalkyl group;

[0098] (2) 1 oxo group;

[0099] (3) 1-2 OH groups;

[0100] (4) 1-2 C_{1-10}alkoxy groups, each optionally substituted with: up to five halo or a perhaloalkoxy, 1 OH or CO_2R^a group;

[0101] (5) 1 CO_2R^a or $S(O)_pR^d$;

[0102] (6) 1-2 Aryl, Hetcy or HAR groups, each optionally substituted as follows:

[0103] (a) 1-5 halo groups,

[0104] (b) 1 OH, CO_2R^a, CN, $S(O)_pR^d$, NO_2 or $C(O)NR^bR^c$,

[0105] (c) 1-2 C_{1-10}alkyl or alkoxy groups, each optionally substituted with: 1-5 halo, up to perhaloalkyl, and 1-2 OH or CO_2R^a groups; and

[0106] (d) 1-2 phenyl rings, each of which is optionally substituted as follows: 1-5 halo groups up to perhalo, 1-3 C_{1-10}alkyl or alkoxy groups, each being further optionally substituted with 1-5 halo up to perhalo, or 1-2 hydroxy or CO_2R^a groups;

[0107] c) Aryl, HAR, Hetcy, —O-Aryl, —O-HAR and —O-Hetcy, each optionally substituted as set forth below:

[0108] (1) 1-3 C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl groups optionally substituted with 1-5 halo groups; 1-2 OH groups; phenyl optionally substituted with 1-3 halo, C_{1-6}alkyl or C_{1-6} alkoxy groups, the alkyl and alkoxy groups being further optionally substituted with 1-3 halo groups; CO_2R^a; CN or $S(O)_pR^d$ groups; and

[0109] (2) 1-3 C_{1-10}alkoxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups, 1-2 OH; phenyl optionally substituted with 1-3 halo, C_{1-6}alkyl or C_{1-6} alkoxy groups, the alkyl and alkoxy groups being further optionally substituted with 1-3 halo groups; CO_2R^a; CN or $S(O)_pR^d$ groups;

said Aryl, HAR, Hetcy —O-Aryl, —O-HAR and —O-Hetcy group c) being further optionally substituted on carbon by a group selected from the group consisting of;

[0110] (3) 1-5 halo groups;

[0111] (4) 1-2 OH groups;

[0112] (5) 1 $S(O)_pR^d$, NO_2 or CN group;

[0113] (6) 1-2 CO_2R^a;

[0114] (7) —$C(O)NR^bR^c$;

each R^2 represents H or is independently selected from the group consisting of:

[0115] a) OH, halo, CO_2R^a, $C(O)NR^bR^c$, NR^bR^c, CN or $S(O)_pR^d$;

[0116] b) C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, OC_{1-10}alkyl, OC_{3-10}alkenyl and OC_{3-10}alkynyl, said groups being optionally substituted with:

[0117] (1) 1-5 halo groups up to a perhaloalkyl group;

[0118] (2) 1 oxo group;

[0119] (3) 1 OH group;

[0120] (4) 1 C_{1-10}alkoxy group, each optionally substituted with: up to five halo or a perhaloalkoxy, 1 OH or CO_2R^a group;

[0121] (5) 1 CO_2R^a or $S(O)_pR^d$;

[0122] (6) 1 Aryl, Hetcy or HAR group, each optionally substituted as follows:

[0123] (a) 1-5 halo groups,

[0124] (b) 1 OH, CO_2R^a, CN, $S(O)_pR^d$, NO_2 or $C(O)NR^bR^c$,

[0125] (c) 1-2 C_{1-10}alkyl or alkoxy groups, each optionally substituted with: 1-5 halo, up to perhaloalkyl, and 1-2 OH or CO_2R^a groups; and

[0126] (d) 1-2 phenyl rings, each of which is optionally substituted as follows: 1-5 halo groups up to perhalo; 1-3 C_{1-10}alkyl or alkoxy groups, each being further optionally substituted with 1-5 halo up to perhalo; and 1-2 hydroxy or CO_2R^a groups;

[0127] c) Aryl, HAR, Hetcy, —O-Aryl, —O-HAR and —O-Hetcy,-each optionally substituted as set forth below:

[0128] (1) 1-3 C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl groups optionally substituted with 1-5 halo groups, 1-2 OH, phenyl, CO_2R^a, CN or $S(O)_pR^d$ groups;

[0129] (2) 1-3 C_{1-10}alkoxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups, 1-2 OH, phenyl, CO_2R^a, CN or $S(O)_pR^d$ groups; said Aryl, HAR or Hetcy group c) being further optionally substituted on carbon by a group selected from the group consisting of;

[0130] (3) 1-5 halo groups up to perhalo;

[0131] (4) 1 OH group;

[0132] (5) 1 $S(O)_pR^d$, NO_2 or CN group;

[0133] (6) 1 CO_2R^a;

[0134] R^3 is selected from the group consisting of:

[0135] a) C_{1-10}alkyl or C_{2-10}alkenyl, each optionally substituted with

[0136] 1-5 halo groups up to perhalo;

[0137] 1-2 OH, C_{3-10}alkoxy or haloC_{1-3}alkoxy groups;

[0138] 1-2 NR^cR^d groups; and

[0139] 1-2 Aryl, HAR or Hetcy groups, each optionally substituted with 1-3 halo groups and 1-2 groups selected from CN, NO_2, C_{1-3}alkyl, haloC_{1-3}alkyl, C_{1-3}alkoxy and haloC_{1-3}alkoxy groups,

[0140] b) Aryl, HAR or Hetcy, each optionally substituted with 1-3 halo groups and 1-2 groups selected from CN, NO_2, C_{1-3}alkyl, haloC_{1-3}alkyl, C_{1-3}alkoxy and haloC_{1-3}alkoxy groups;

[0141] R^4 is independently selected from the group consisting of: Aryl, HAR or Hetcy, each optionally substituted as set forth below:

[0142] (1) 1-3 $C\text{-}_{1-14}$alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl groups optionally substituted with 1-5 halo groups, 1-2 OH, CO_2R^a, CN or $S(O)_pR^d$ groups or phenyl optionally substituted as follows: 1-5 halo groups up to perhalo; 1-3 C_{1-10}alkyl or alkoxy groups, each being further optionally substituted with 1-5 halo up to perhalo, or 1-2 hydroxy or CO_2R^a groups;

[0143] (2) 1-3 C_{1-10}alkoxy or C_{3-10}alkenyloxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups, 1-2 OH, CO_2R^a, CN, $S(O)_pR^d$, and phenyl optionally substituted as follows: 1-5 halo groups up to perhalo; 1-3 C_{1-10}alkyl or alkoxy groups, each being further optionally substituted with 1-5 halo up to perhalo, or 1-2 hydroxy or CO_2R^a groups;

[0144] (3) 1-2 Aryl, HAR or Hetcy, OAryl, OHAR or OHetcy groups, each optionally substituted as follows:

[0145] (i) 1-3 halo groups;

[0146] (ii) 1-2 C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl groups each optionally substituted with 1-5 halo groups, 1-2 OH, phenyl, CO_2R^a, CN or $S(O)_pR^d$ groups;

[0147] (iii) 1-2 C_{1-10}alkoxy groups the alkyl portion of which being optionally substituted with 1-5 halo groups, 1-2 OH, phenyl, CO_2R^a, CN or $S(O)_pR^d$ groups; and

[0148] (iv) 1-2 CO_2R^a, $S(O)_pR^d$, CN, NR^bR^c, NO_2 or OH groups;

said Aryl, HAR or Hetcy group R^4 being further optionally substituted on carbon by a group selected from the group consisting of;

[0149] (4) 1-5 halo groups;

[0150] (5) 1-2 OH groups;

[0151] (6) 1 $S(O)_pR^d$, NO_2 or CN group;

[0152] (7) 1-2 CO_2R^a;

[0153] R^5 represents H or C_1-6alkyl;

[0154] R^6 is selected from the group consisting of H, OH, F or C_{1-3}alkyl;

[0155] R^7 is H or F, or R^6 and R^7 are taken in combination and represent oxo;

[0156] R^8 represents H or C_{1-6}alkyl, optionally substituted with OH and 1-5 halo groups up to perhalo;

[0157] R^9 represents H, halo, OH, C_{1-6}alkyl, optionally substituted with 1-5 halo groups up to perhalo, or C_{1-6}alkoxy, optionally substituted with 1-3 halo groups up to perhalo,

or when R^9 is ortho to the benzylic group, R^8 and R^9 can be taken together and represent a —$(CH_2)_{2-4}$— or a —O—$(CH_2)_{1-3}$— group;

[0158] R^a is H or C, loalkyl, optionally substituted with phenyl, OH, OC_{1-6}alkyl, CO_2H, CO_2C_{1-6}alkyl and 1-3 halo groups;

[0159] R^b is H or C_{1-10}alkyl;

[0160] R^c is H or is independently selected from:

[0161] (a) C_{1-10}alkyl, optionally substituted with OH, OC_{1-6}alkyl, CO_2H, CO_2C_{1-6}alkyl, and 1-3 halo groups;

[0162] (b) Aryl or Ar—C_{1-6}alkyl, each optionally substituted with 1-5 halos and 1-3 members selected from the group consisting of: CN, OH, C_{1-10}alkyl and OC_{1-10}alkyl, said alkyl and alkoxy being further optionally substituted with 1-5 halo groups up to perhalo;

[0163] (c) Hetcy or Hetcy-C_{1-6}alkyl, optionally substituted with 1-5 halo groups and 1-3 groups selected from: oxo, C_{1-10}alkyl and OC_{1-10}alkyl, said alkyl and alkoxy being further optionally substituted with 1-5 halo groups up to perhalo; and

[0164] (d) HAR or HAR-C_{1-6}alkyl, optionally substituted with 1-5 halo groups and 1-3 groups selected from: C_{1-10}alkyl and OC_{1-10}alkyl, said alkyl and alkoxy being further optionally substituted with 1-5 halo groups up to perhalo;

[0165] R^d is C_{1-10}alkyl, Aryl or Ar—C_{1-10}alkyl;

[0166] m is an integer selected from 0, 1 and 2;

[0167] n is an integer selected from 0 to 6;

[0168] p is an integer selected from 0, 1 and 2, and

[0169] when at least one of m and n is other than 0, Z is selected from CO_2R^a, 5-tetrazolyl and 5-(2-oxo-1,3,4-oxadiazolyl), and when both m and n are 0, Z is selected from 5-tetrazolyl and 5-(2-oxo-1,3,4-oxadiazolyl).

[0170] One aspect of the invention that is of interest relates to a compound of formula I or a pharmaceutically acceptable salt or solvate there of, wherein R^a is selected from the group consisting of: H, halo, C_{1-10}alkyl and OC_{1-10}alkyl, said alkyl and O-alkyl groups being optionally substituted with 1-5 halo groups up to a perhaloalkyl or perhaloalkoxy. Within this subset, all other variables are as originally defined with respect to formula I.

[0171] More particularly, an aspect of the invention that is of interest relates to compounds of formula I or a pharmaceutically acceptable salt or solvate thereof, wherein, R^1 is selected from the group consisting of: H, halo, C**1-4**alkyl, C**1-4**alkoxy, said alkyl and alkoxy being optionally substituted with 1-3 halo groups. Within this subset, all other variables are as originally defined with respect to formula I.

[0172] Another aspect of the invention that is of interest relates to compounds of formula I wherein each R^2 represents H or is independently selected from the group consisting of:

[0173] a) halo or $S(O)_pR^d$; wherein p is 2 and R^d represents C_{1-10}alkyl;

[0174] b) C_{1-10}alkyl, C_{2-10}alkenyl, OC_{1-10}alkyl and OC_{3-10}alkenyl, said groups being optionally substituted with:

[0175] (1) 1-5 halo groups up to a perhaloalkyl group;

[0176] (2) 1 C_{1-10}alkoxy group, each optionally substituted with: up to five halo or perhaloalkoxy, 1 OH or CO_2R^a group;

[0177] (3) 1 Aryl or HAR group, each optionally substituted as follows:

[0178] (a) 1-5 halo groups,

[0179] (b) 1-2 C_{1-10}alkyl or alkoxy groups, each optionally substituted with: 1-5 halo, up to perhaloalkyl, and 1-2 OH or CO_2R^a groups;

[0180] c) Aryl or HAR, each optionally substituted with:

[0181] (1) 1-2 C_{1-10}alkyl groups optionally substituted with 1-5 halo groups;

[0182] (2) 1-2 C_{1-10}alkoxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups;

said Aryl or HAR being further optionally substituted on carbon by 1-3 halo groups; up to perhalo. Within this subset, all other variables are as originally defined with respect to formula I.

[0183] More particularly, an aspect of the invention that is of interest relates to compounds of formula I wherein one R^2 group represents H and the other represents H or is selected from the group consisting of:

[0184] a) halo or $S(O)_pR^d$; wherein p is 2 and R^d represents C_{1-10}-alkyl;

[0185] b) C_{1-10}alkyl, C_{2-10}alkenyl, OC_{1-10}alkyl or OC_{3-10}alkenyl, said groups being optionally substituted with:

[0186] (1) 1-5 halo groups up to a perhaloalkyl group;

[0187] (2) 1 C_{1-10}alkoxy group, each optionally substituted with: up to five halo or a perhaloalkoxy, 1 OH or CO_2R^a group;

[0188] (3) 1 Aryl or HAR group, each optionally substituted as follows:

[0189] (a) 1-5 halo groups,

[0190] (b) 1-2 C_{1-10}alkyl or alkoxy groups, each optionally substituted with: 1-5 halo, up to perhaloalkyl, and 1-2 OH or CO_2R^agroups;

[0191] c) Aryl or HAR, each optionally substituted with:

[0192] (1) 1-2 C_{1-10}alkyl groups optionally substituted with 1-5 halo groups;

[0193] (2) 1-2 C_{1-10}alkoxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups;

said Aryl or HAR being further optionally substituted on carbon by 1-3 halo groups; up to perhalo. Within this subset, all other variables are as originally defined with respect to formula I.

[0194] Even more particularly, an aspect of the invention that is of interest relates to a compound of formula I wherein:

[0195] one R^2 group represents H and the other represents H or a member selected from the group consisting of:

[0196] a) halo or $S(O)_pR^d$; wherein p is 2 and R^d represents C_{1-2}alkyl;

[0197] b) C_{1-4}alkyl, C_{2-4}alkenyl, OC_{1-4}alkyl or OC_{3-4}alkenyl, said groups being optionally substituted with:

[0198] (1) 1-5 halo groups up to a perhaloalkyl group;

[0199] (2) 1 C_{1-4}alkoxy group, optionally substituted with: up to 3 halo or a perhaloalkoxy group;

[0200] (3) 1 Aryl or HAR group, each optionally substituted as follows:

[0201] (a) 1-3 halo groups,

[0202] (b) 1 C_{1-4}alkyl or alkoxy group, each optionally substituted with: 1-3 halo, up to perhaloalkyl, groups;

[0203] c) Aryl or HAR, each optionally substituted with:

[0204] (1) 1-2 C_{1-4}alkyl groups optionally substituted with 1-3 halo groups;

[0205] (2) 1-2 C_{1-4}alkoxy groups, the alkyl portion of which is optionally substituted with 1-3 halo groups;

said Aryl or HAR being further optionally substituted on carbon by 1-3 halo groups; up to perhalo. Within this subset, all other variables are as originally defined with respect to formula I.

[0206] Another aspect of the invention that is of interest relates to compounds of formula I wherein R^3 is selected from the group consisting of:

[0207] a) C_{1-6}alkyl optionally substituted with:

[0208] 1-3 halo groups up to perhalo;

[0209] 1 OH, C_{1-3}alkoxy or haloC_{1-3}alkoxy group;

[0210] 1 NR^cR^d group; and

[0211] 1 Aryl or HAR group, each optionally substituted with 1-3 halo groups and 1-2 groups selected from C_{1-3}alkyl, haloC_{1-3}alkyl, C_{1-3}alkoxy and haloC_{1-3}alkoxy groups,

[0212] b) Aryl or HAR, each optionally substituted with 1-3 halo groups and 1-2 groups selected from C_{1-3}alkyl, haloC_{1-3}alkyl, C_{1-3}alkoxy and haloC_{1-3}alkoxy groups. Within this subset, all other variables are as originally defined with respect to formula I.

[0213] More particularly, an aspect of the invention that is of interest relates to compounds of formula I wherein R^3 is selected from the group consisting of:

[0214] a) C_{1-6}alkyl optionally substituted with:

[0215] 1-3 halo groups up to perhalo;

[0216] 1 C_{1-3}alkoxy or haloC_{1-3}alkoxy group,

[0217] 1 NR^cR^d group; wherein R^c and R^d are independently selected from H, C_{1-3}alkyl and phenyl; and

[0218] 1 Aryl or HAR group, each optionally substituted with 1-3 halo groups and 1-2 groups selected from C_{1-3}alkyl, haloC_{1-3}alkyl, C_{1-3}alkoxy and haloC_{1-3}alkoxy groups,

[0219] b) Aryl or HAR, each optionally substituted with 1-3 halo groups and 1 group selected from: C_{1-3}alkyl, haloC_{1-3}alkyl, C_{1-3}alkoxy and haloC_{1-3}alkoxy. Within this subset, all other variables are as originally defined with respect to formula I.

[0220] Another aspect of the invention that is of interest relates to compounds of formula I or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0221] R^4 represents an Aryl or HAR group, each optionally substituted as set forth below:

[0222] (1) 1-2 C_{1-10}alkyl or C_{2-10}alkenyl groups, which are optionally substituted with 1-3 halo groups, or phenyl optionally substituted with 1-2 halo, C_{1-4}alkyl or alkoxy groups, each being further optionally substituted with 1-3 halo groups;

[0223] (2) 1-2 C_{1-10}alkoxy or C_{3-10}alkenyloxy groups, which are optionally substituted with 1-3 halo groups, 1-2 OH or $S(O)_pR^d$, and phenyl optionally substituted as follows: 1-3 halo groups up to perhalo; 1-2 C_{1-6}alkyl or alkoxy groups, each being further optionally substituted with 1-3 halo up to perhalo, or 1-2 hydroxy or CO^2R^a groups;

[0224] (3) 1-2 Aryl, HAR or Hetcy, OAryl, OHAR or OHetcy groups, each optionally substituted as follows:

[0225] (i) 1-3 halo groups;

[0226] (ii) 1-2 C_{1-3}alkyl or C_{2-4}alkenyl groups each optionally substituted with 1-3 halo groups, and 1 of OH, phenyl, CO_2R^a, CN and $S(O)_pR^d$;

[0227] (iii) 1-2 C_{1-3}alkoxy groups the alkyl portion of which being optionally substituted with 1-3 halo groups, and 1 of OH, phenyl, CO_2R^a, CN or $S(O)_pR^d$; and

[0228] (iv) 1-2 CO_2R^a, $S(O)_pR^d$, CN, NR^bR^c, NO_2 or OH groups;

said Aryl, HAR or Hetcy group R^4 being further optionally substituted on carbon by a group selected from the group consisting of;

[0229] (4) 1-5 halo groups;

[0230] (5) 1-2 OH groups;

[0231] (6) 1 $S(O)_pR^d$, NO_2 or CN group. Within this subset, all other variables are as originally defined with respect to formula I.

[0232] In another aspect of the invention that is of interest, R^5 represents H or CH_3. Within this subset, all other variables are as originally defined with respect to formula I.

[0233] In another aspect of the invention that is of interest, R^8 is selected from the group consisting of H and C_{1-3}alkyl. Within this subset, all other variables are as originally defined with respect to formula I.

[0234] In another aspect of the invention that is of interest, R^6 and R^7 represent H. Within this subset, all other variables are as originally defined with respect to formula I.

[0235] In another aspect of the invention that is of interest, R^9 represents H. Within this subset, all other variables are as originally defined with respect to formula I.

[0236] In another aspect of the invention that is of interest, m is 0 and n is an integer selected from 0 to 2. Within this subset, all other variables are as originally defined with respect to formula I.

[0237] In another aspect of the invention when n is 1 or 2, Z is selected from CO_2R^a and 5-tetrazolyl, when both m and n are 0, Z is 5-tetrazolyl. Within this subset, all other variables are as originally defined with respect to formula I.

[0238] More particularly, an aspect of the invention that is of interest relates to a compound of formula I or a pharmaceutically acceptable salt or solvate there of, wherein:

[0239] R^1 is selected from the group consisting of: H, halo, C_{1-10}alkyl and OC_{1-10}alkyl, said alkyl and O-alkyl groups being optionally substituted with 1-5 halo groups up to a perhaloalkyl or perhaloalkoxy;

[0240] each R^2 represents H or is independently selected from the group consisting of:

[0241] a) halo or $S(O)_pR^d$; wherein p is 2 and R^d represents C_{1-10}alkyl;

[0242] b) C_{1-10}alkyl, C_{2-10}alkenyl, OC_{1-10}alkyl and OC_{3-10}alkenyl, said groups being optionally substituted with:

[0243] (1) 1-5 halo groups up to perhaloalkyl;

[0244] (2) 1 C_{1-10}alkoxy group, each optionally substituted with: up to five halo or perhaloalkoxy, 1 OH or CO_2R^a group;

[0245] (3) 1 Aryl or HAR group, each optionally substituted as follows:

[0246] (a) 1-5 halo groups,

[0247] (b) 1-2 C_{1-10}alkyl or alkoxy groups, each optionally substituted with: 1-5 halo, up to perhaloalkyl, and 1-2 OH or CO_2R^agroups;

[0248] c) Aryl or HAR, each optionally substituted with:

[0249] (1) 1-2 C_{1-10}alkyl groups optionally substituted with 1-5 halo groups;

[0250] (2) 1-2 C_{1-10}alkoxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups;

said Aryl or HAR being further optionally substituted on carbon by 1-3 halo groups; up to perhalo;

[0251] R^3 is selected from the group consisting of:

[0252] a) C_{1-6}alkyl optionally substituted with:

[0253] 1-3 halo groups up to perhalo;

[0254] 1 OH, C_{1-3}alkoxy or haloC_{1-3}alkoxy group;

[0255] 1 NR^cR^d group; and

[0256] 1 Aryl or HAR group, each optionally substituted with 1-3 halo groups and 1-2 groups selected from C_{1-3}alkyl, haloC_{1-3}alkyl, C_{1-3}alkoxy and haloC_{1-3}alkoxy;

[0257] b) Aryl or HAR, each optionally substituted with 1-3 halo groups and 1-2 groups selected from C_{1-3}alkyl, haloC_{1-3}alkyl, C_{1-3}alkoxy and haloC_{1-3}alkoxy;

[0258] R^4 represents an Aryl or HAR group, each optionally substituted as set forth below:

[0259] (1) 1-2 C_{1-10}alkyl or C_{2-10}alkenyl groups, which are optionally substituted with 1-3 halo groups, or phenyl optionally substituted with 1-2 halo, C_{1-4}alkyl or alkoxy groups, each being further optionally substituted with 1-3 halo groups;

[0260] (2) 1-2 C_{1-10}alkoxy or C_{3-10}alkenyloxy groups, which are optionally substituted with 1-3 halo groups, 1-2 OH or $S(O)_pR^d$, and phenyl optionally substituted as follows: 1-3 halo groups up to perhalo; 1-2 C_{1-6}alkyl or alkoxy groups, each being further optionally substituted with 1-3 halo up to perhalo, or 1-2 hydroxy or CO^2R^a groups;

[0261] (3) 1-2 Aryl, HAR or Hetcy, OAryl, OHAR or OHetcy groups, each optionally substituted as follows:

[0262] (i) 1-3 halo groups;

[0263] (ii) 1-2 C_{1-3}alkyl or C_{2-4}alkenyl groups each optionally substituted with 1-3 halo groups, and 1 of OH, phenyl, CO_2R^a, CN and $S(O)_pR^d$;

[0264] (iii) 1-2 C_{1-3}alkoxy groups the alkyl portion of which being optionally substituted with 1-3 halo groups, and 1 of OH, phenyl, CO_2R^a, CN and $S(O)_pR^d$; and

[0265] (iv) 1-2 CO_2R^a, $S(O)_pR^d$, CN, NR^bR^c, NO_2 or OH groups;

said Aryl, HAR or Hetcy group R^4 being further optionally substituted on carbon by a group selected from the group consisting of;

[0266] (4) 1-5 halo groups;

[0267] (5) 1-2 OH groups;

[0268] (6) 1 $S(O)_pR^d$, NO_2 or CN group;

[0269] R^5 represents H or CH_3;

[0270] R^8 is selected from the group consisting of H and C_{1-3}alkyl;

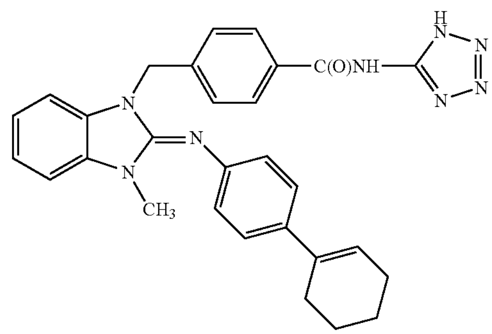
[0271] R^6, R^7 and R^9 represents H;

[0272] m is 0 and n is an integer selected from 0 to 2, such that when n is 1 or 2, Z is selected from CO_2R^a and 5-tetrazolyl, and when both m and n are 0, Z is 5-tetrazolyl. Within this subset, all other variables are as originally defined with respect to formula I.

[0273] Examples of compounds that fall within the present invention include the following:

TABLE 1

1



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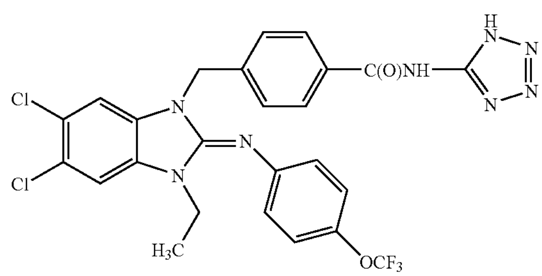

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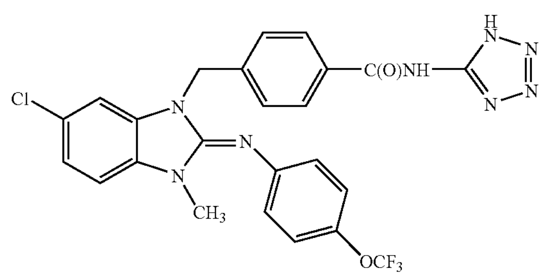

TABLE 1-continued

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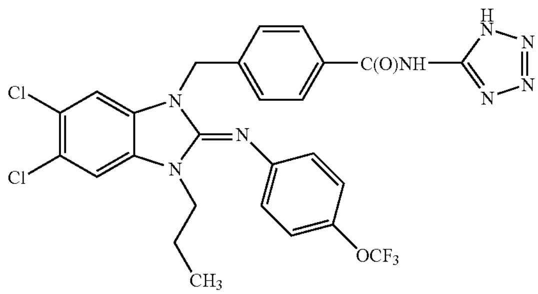

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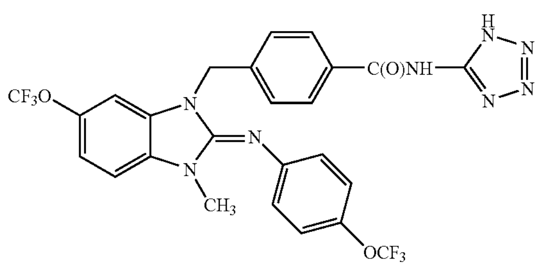

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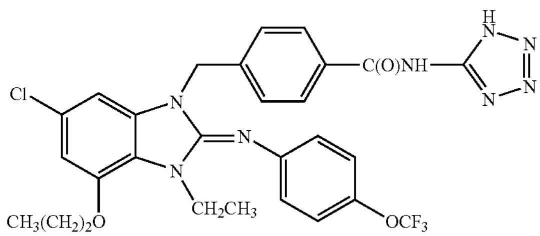

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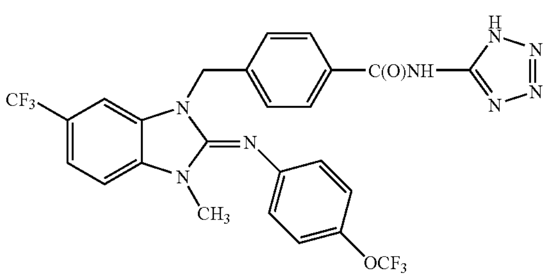

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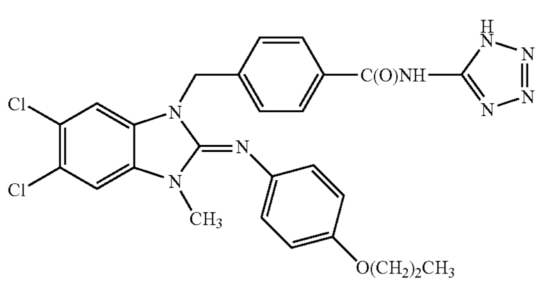

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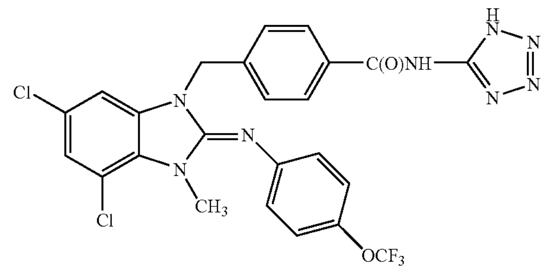

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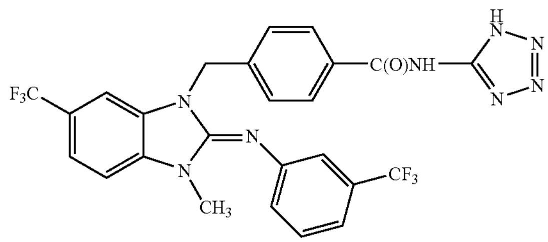

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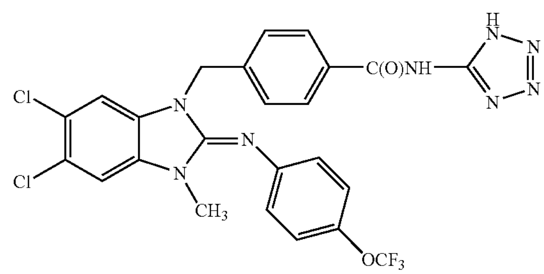

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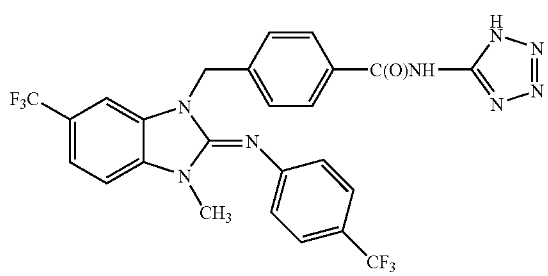

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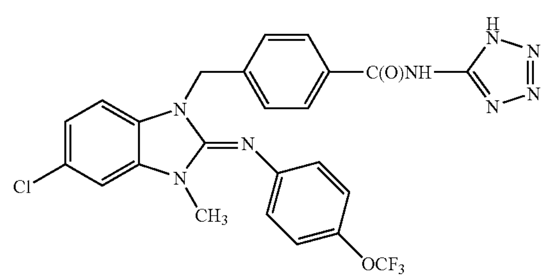

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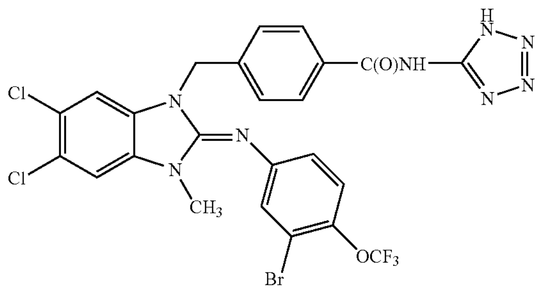

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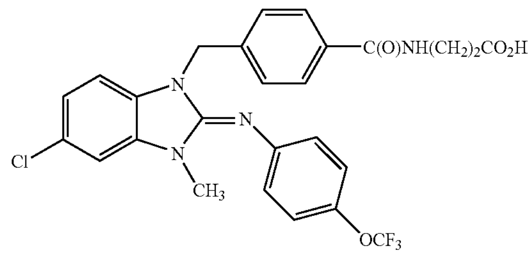

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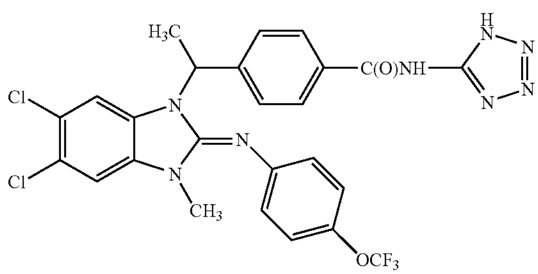

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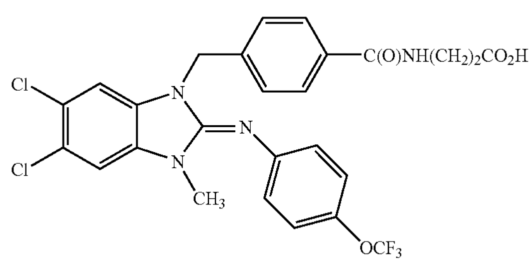

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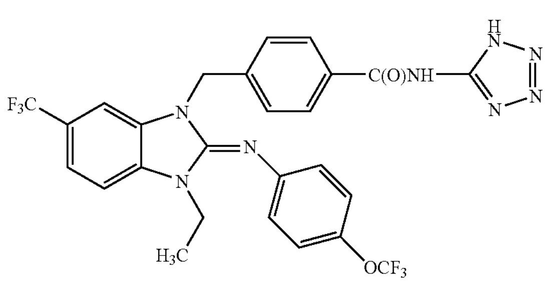

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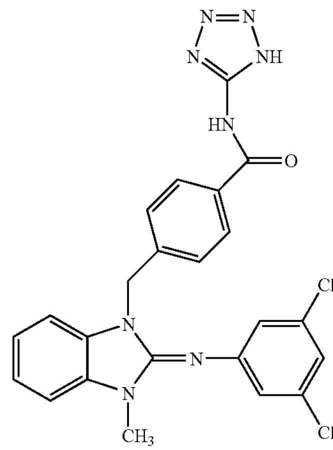

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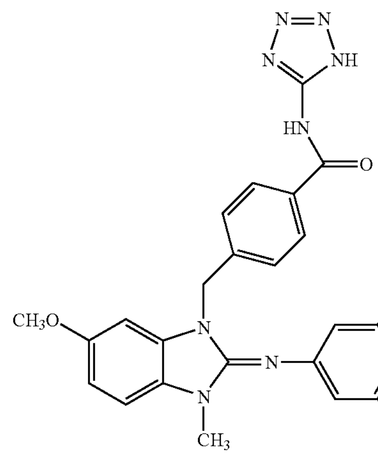

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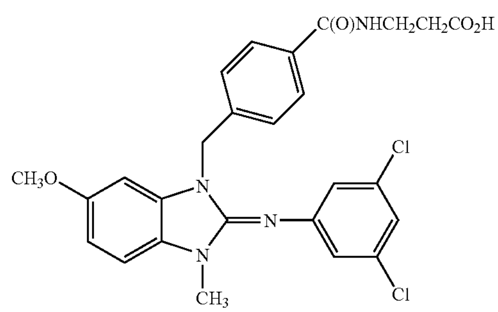

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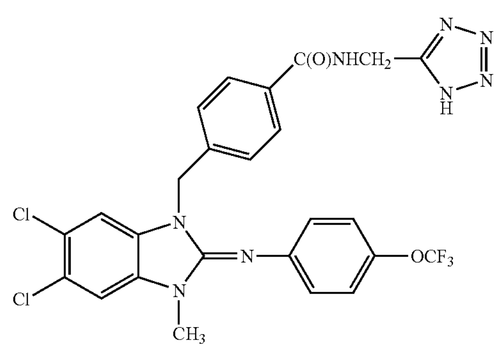

TABLE 1-continued

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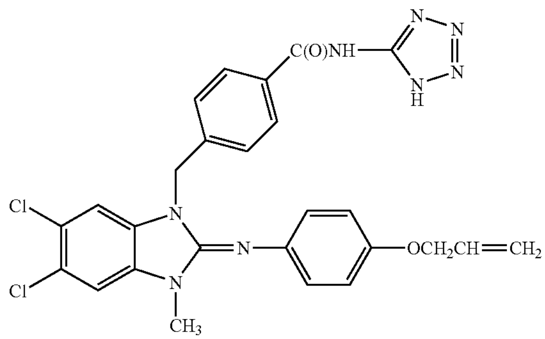

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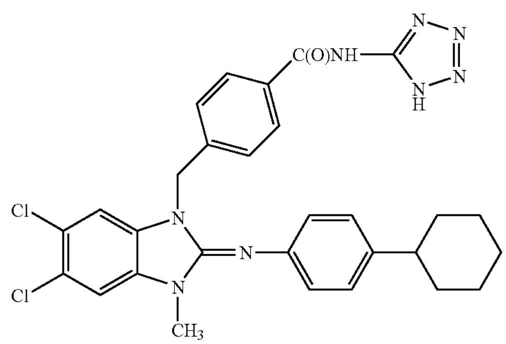

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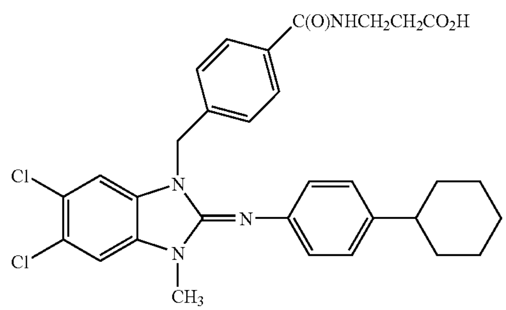

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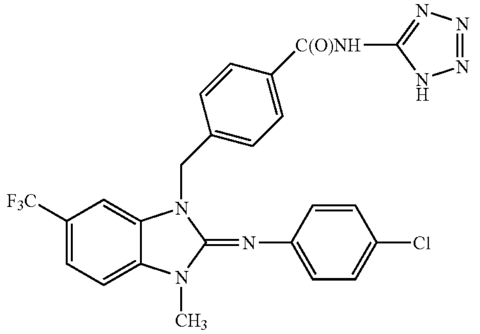

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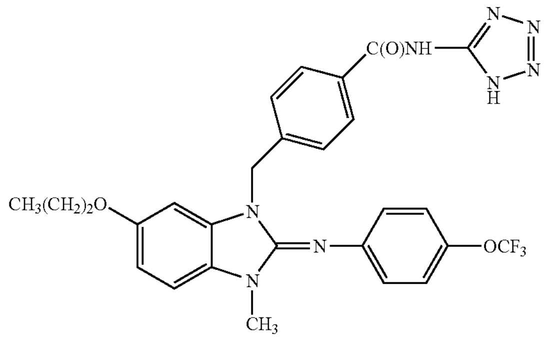

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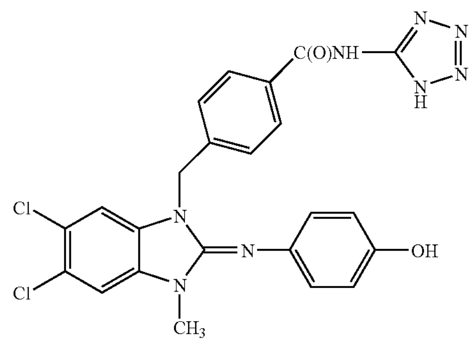

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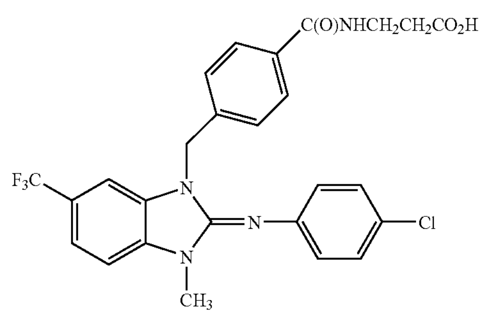

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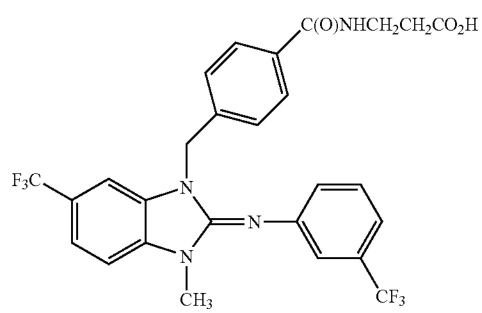

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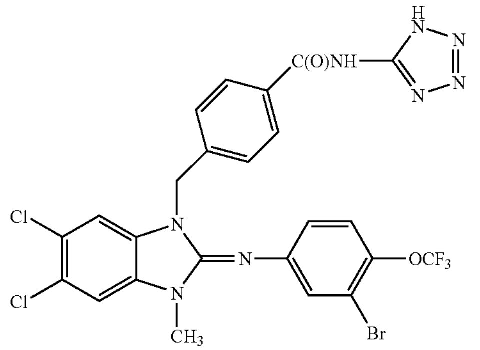

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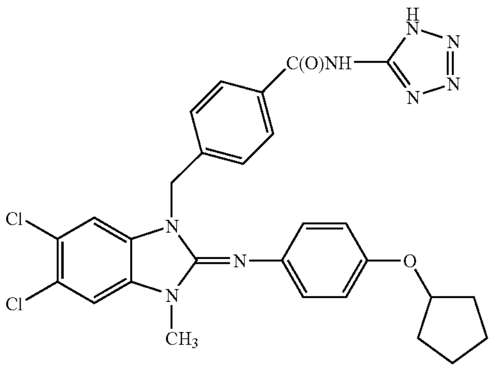

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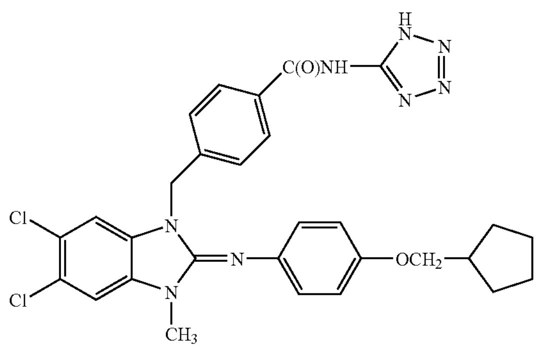

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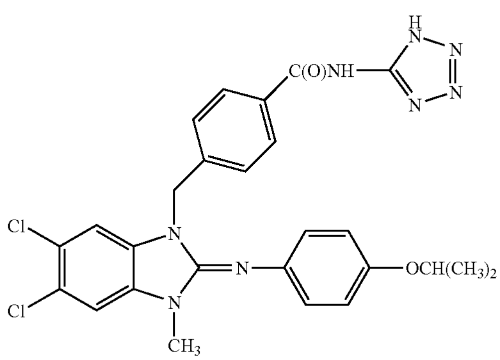

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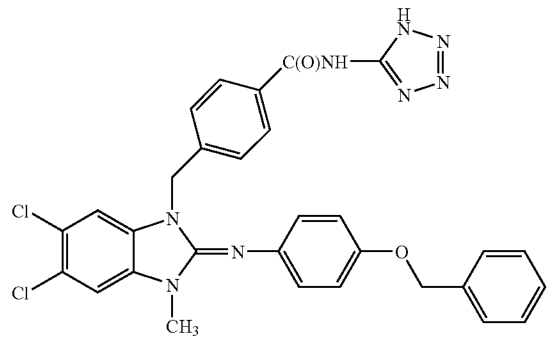

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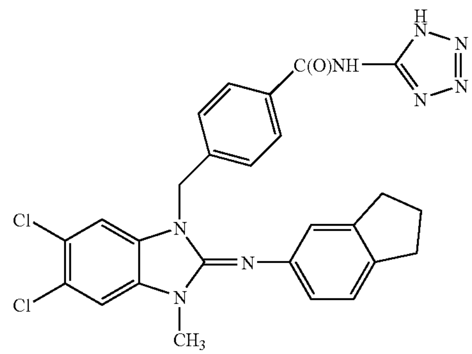

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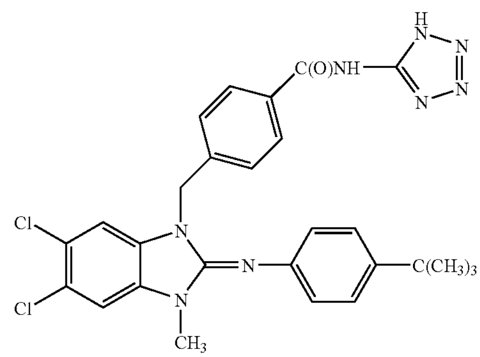

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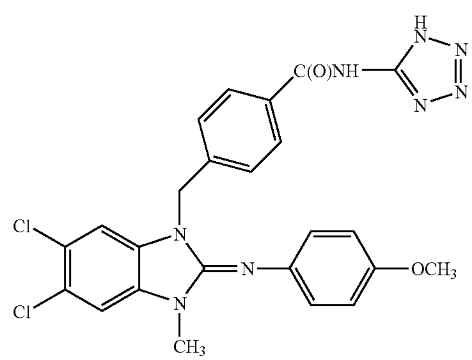

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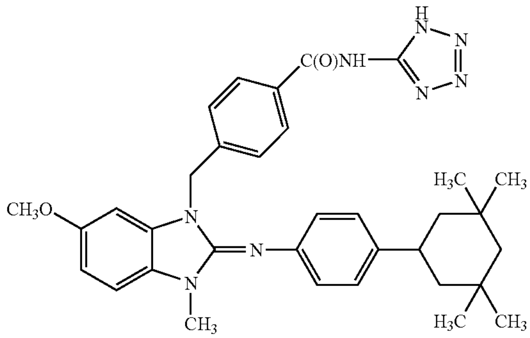

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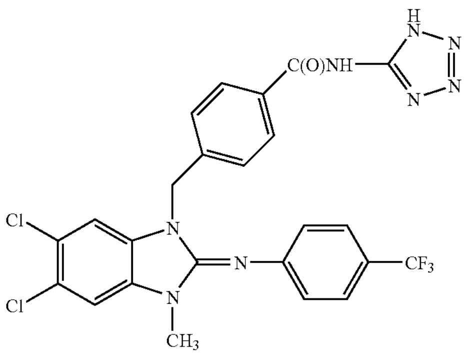

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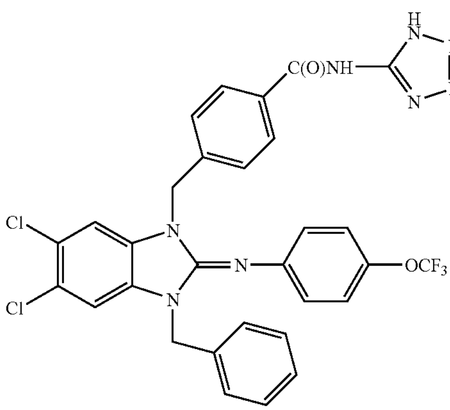

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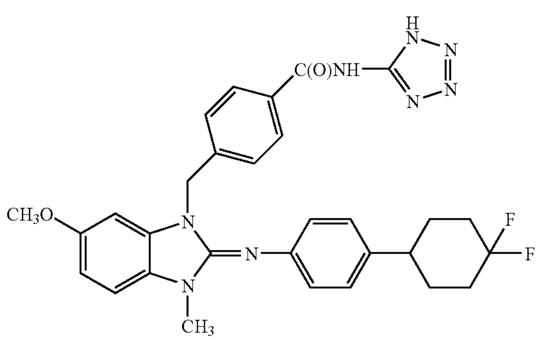

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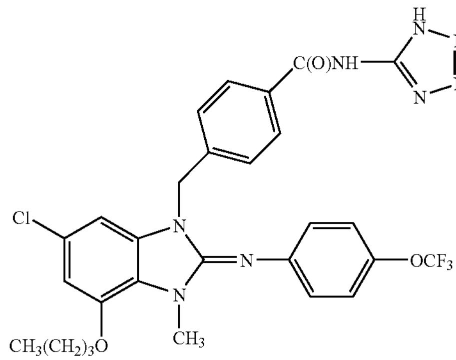

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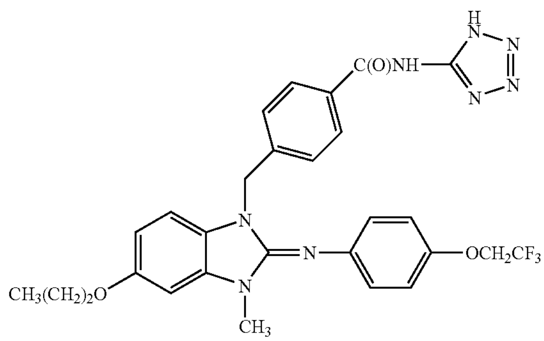

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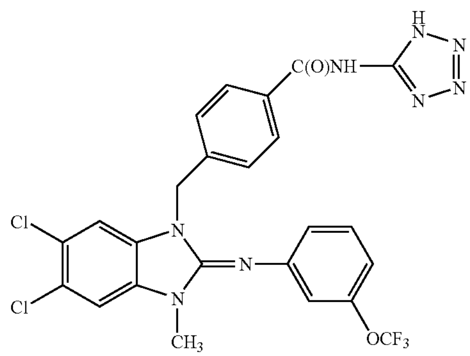

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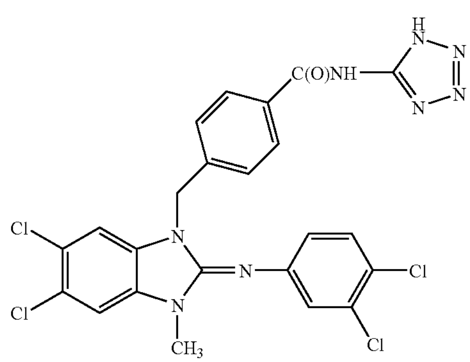

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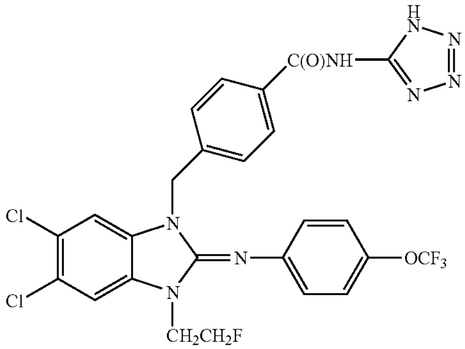

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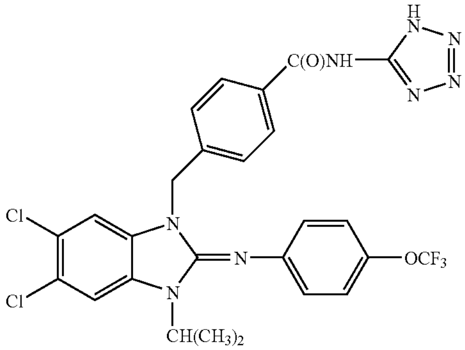

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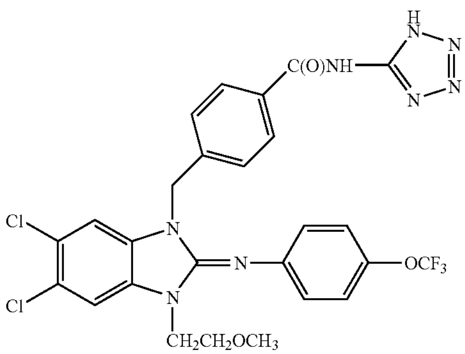

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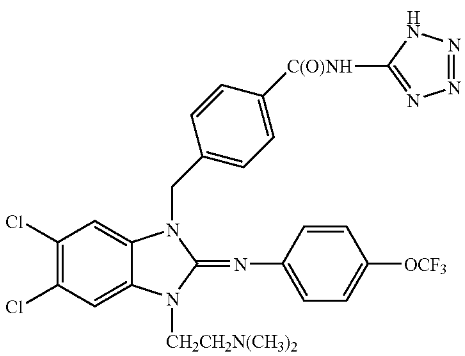

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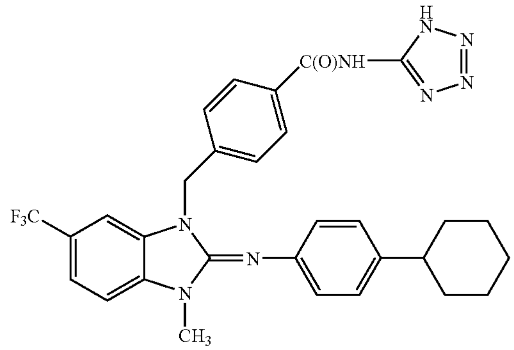

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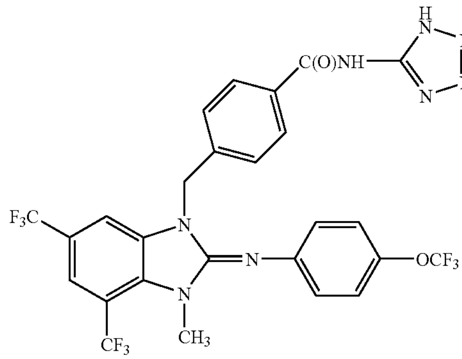

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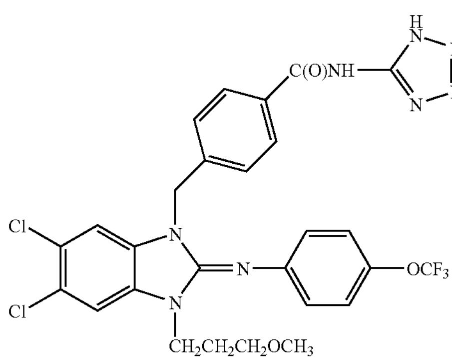

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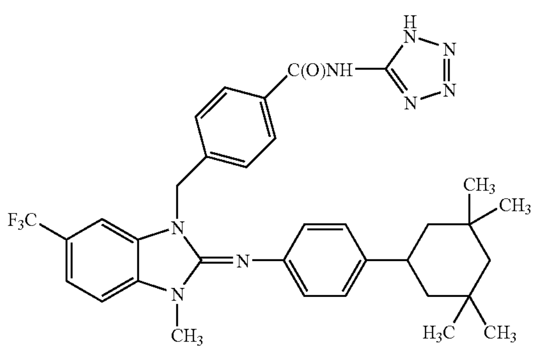

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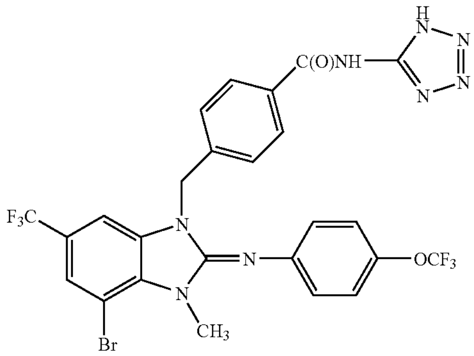

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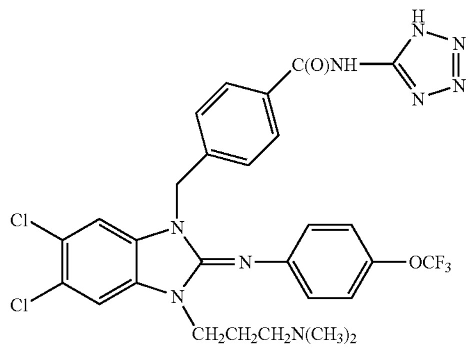

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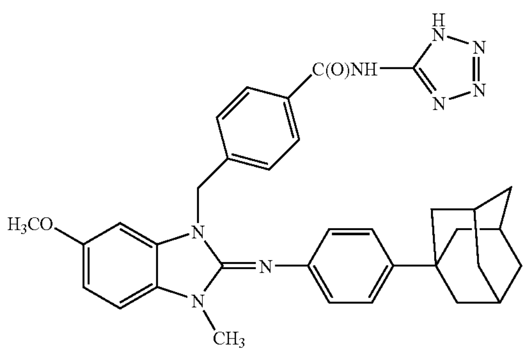

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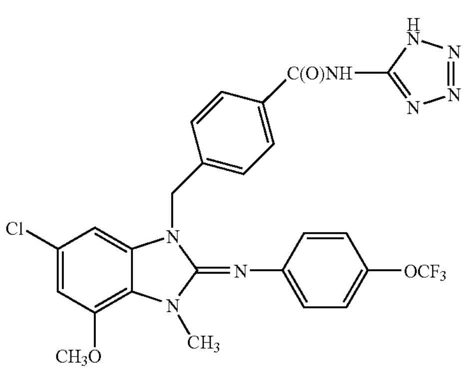

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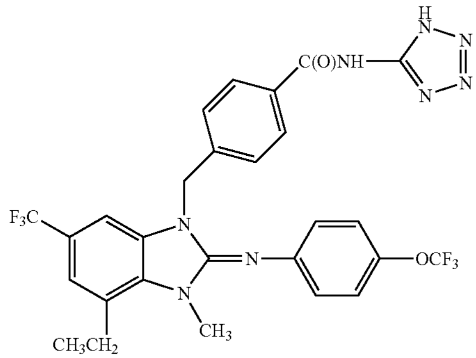

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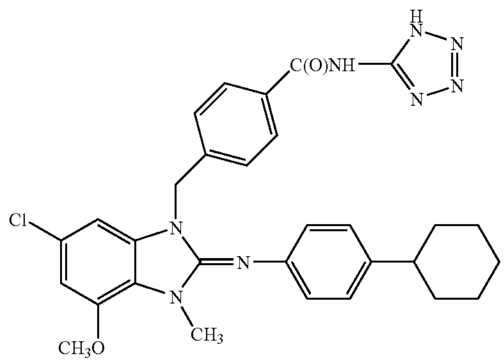

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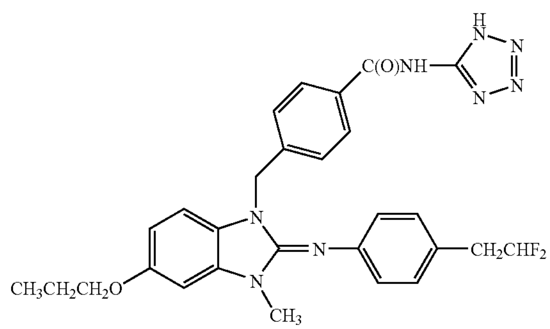

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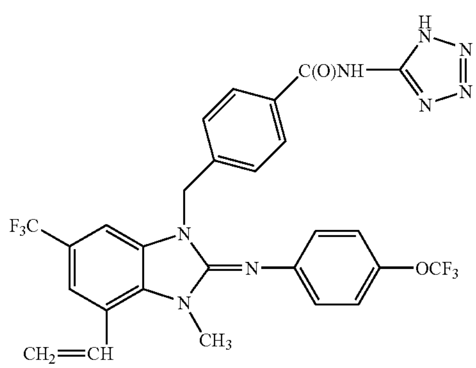

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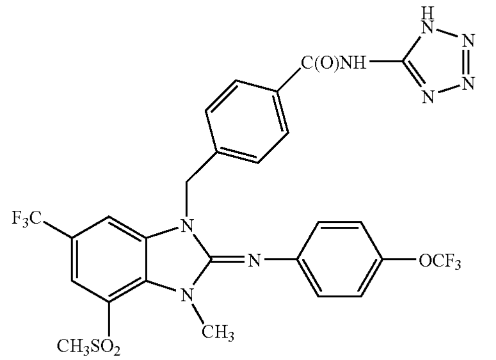

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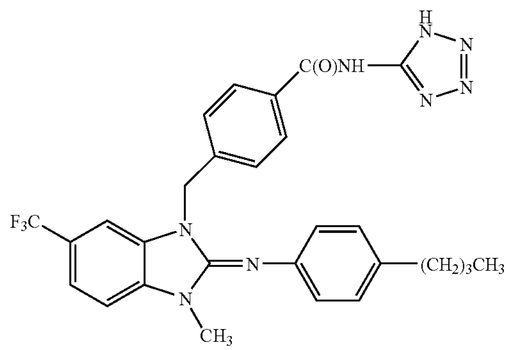

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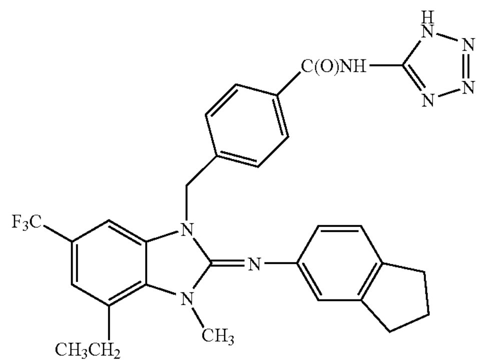

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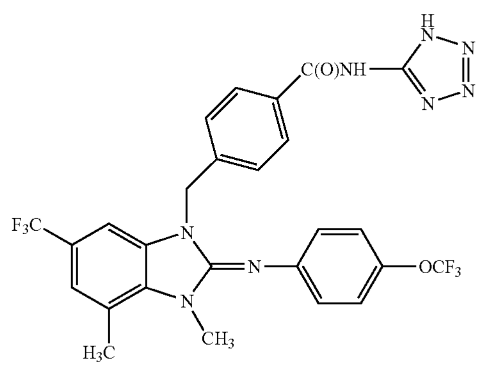

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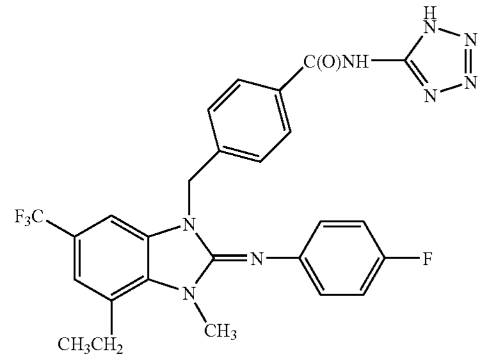

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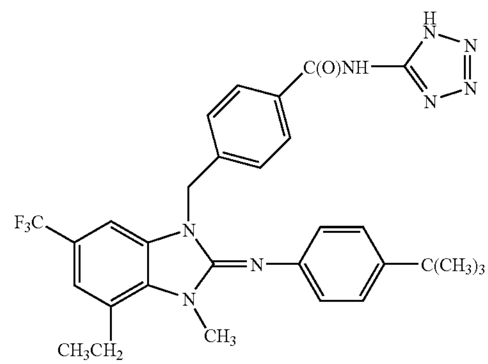

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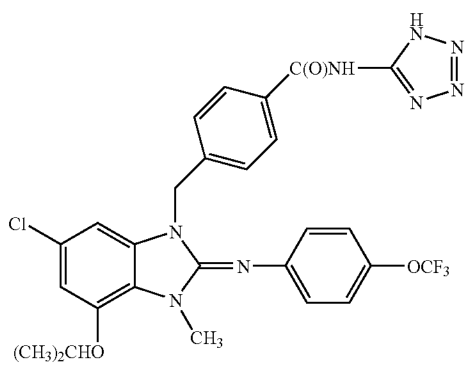

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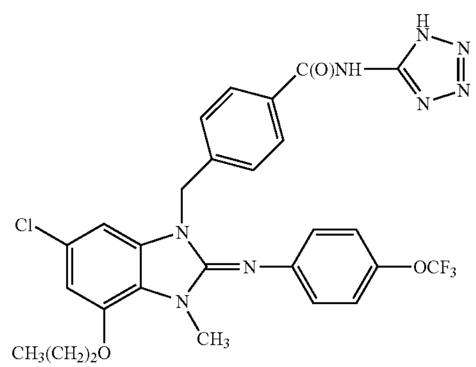

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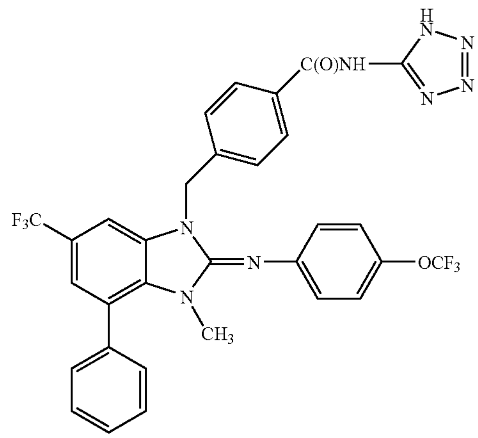

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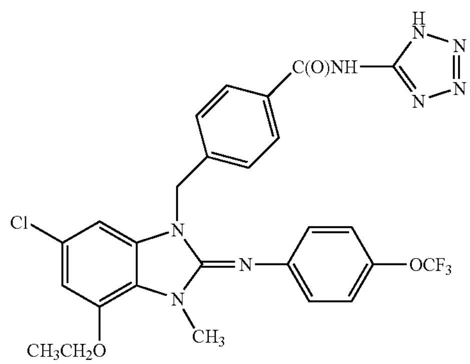

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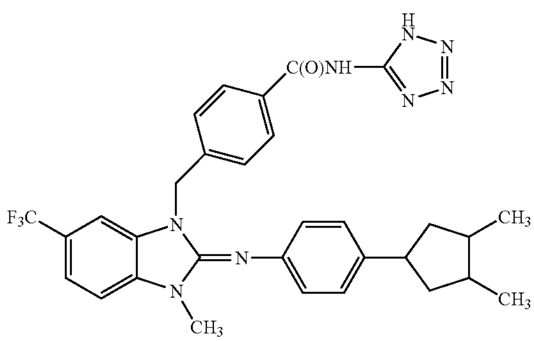

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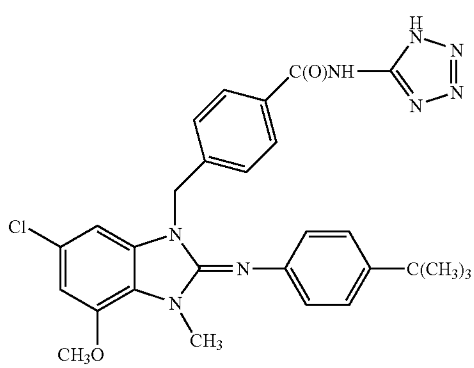

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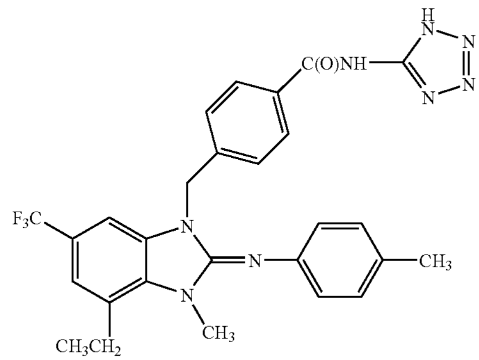

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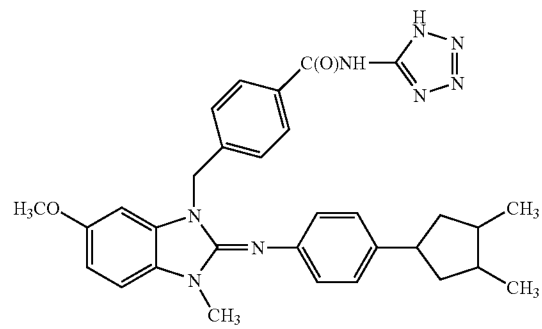

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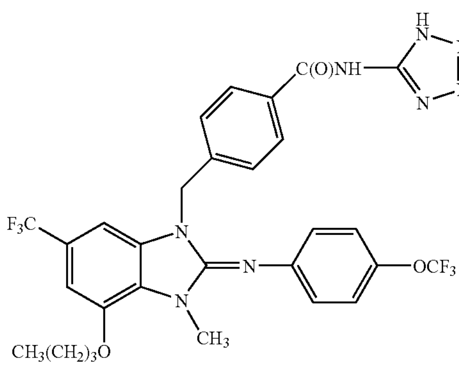

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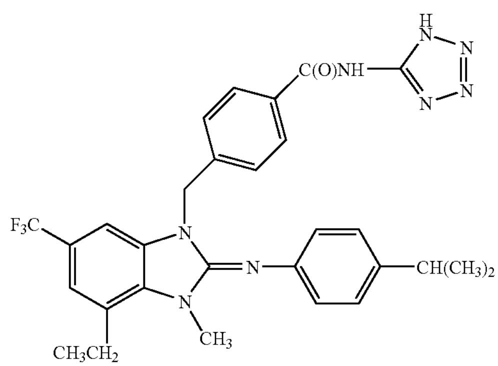

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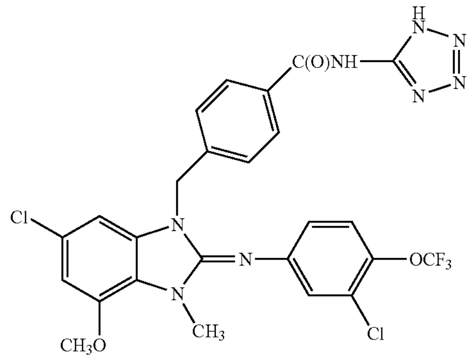

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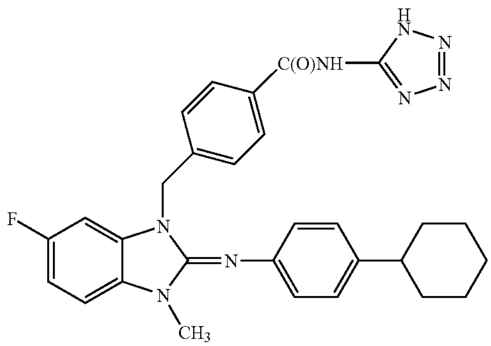

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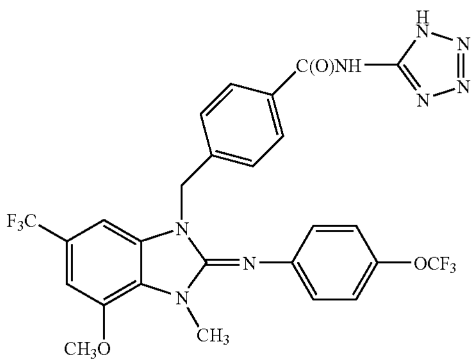

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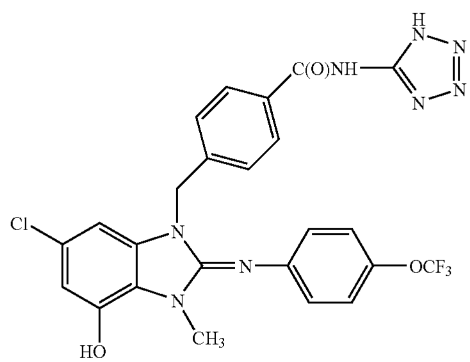

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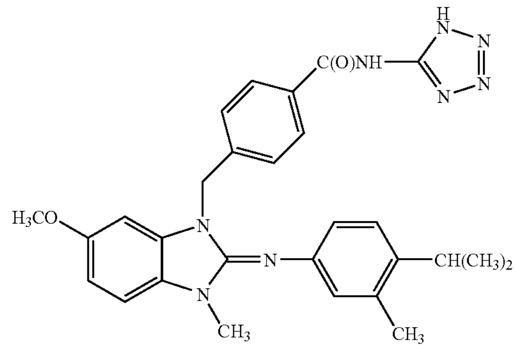

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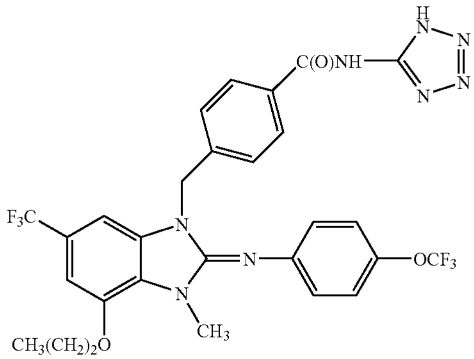

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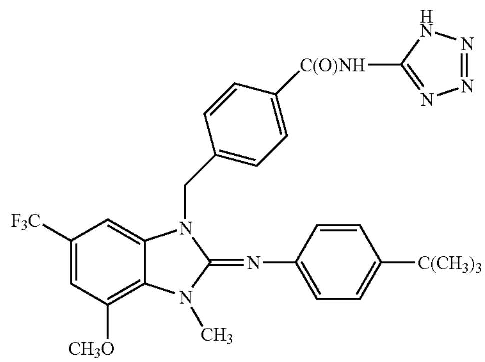

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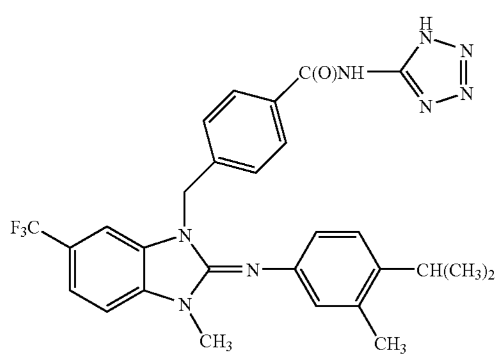

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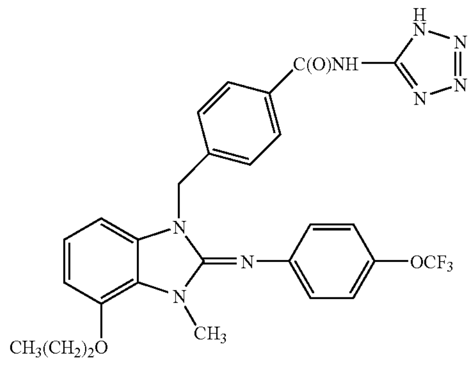

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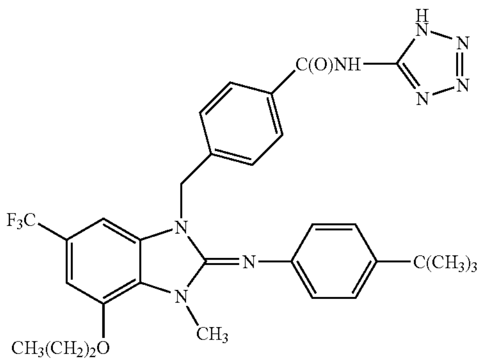

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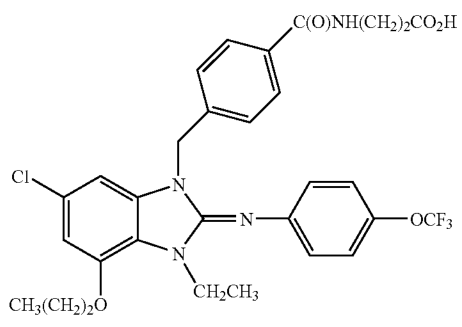

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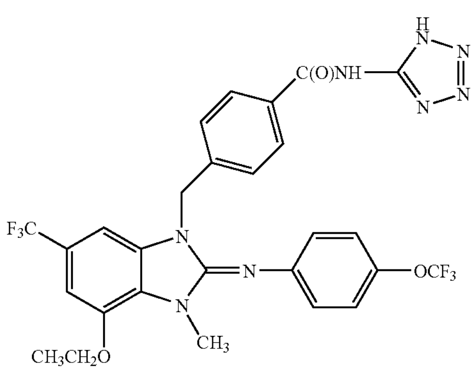

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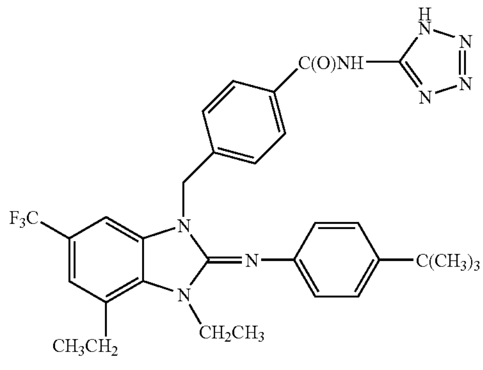

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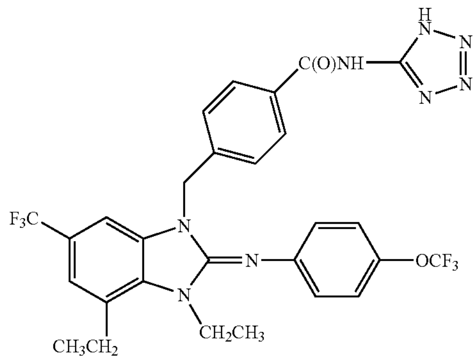

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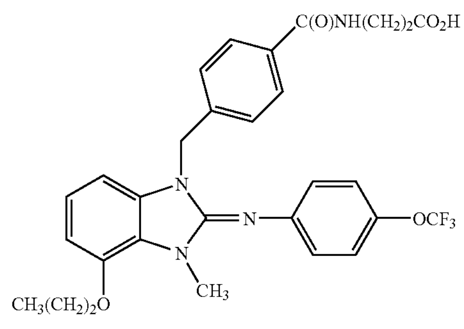

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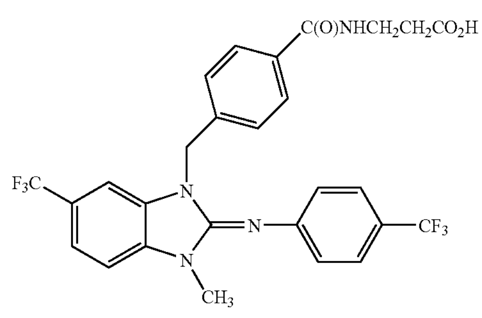

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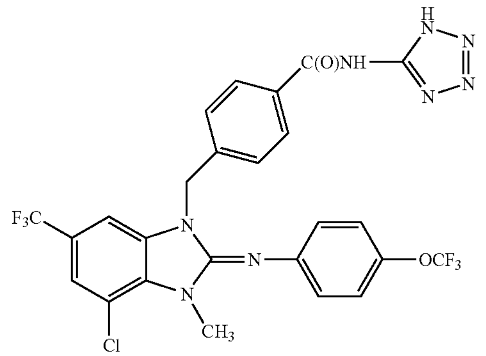

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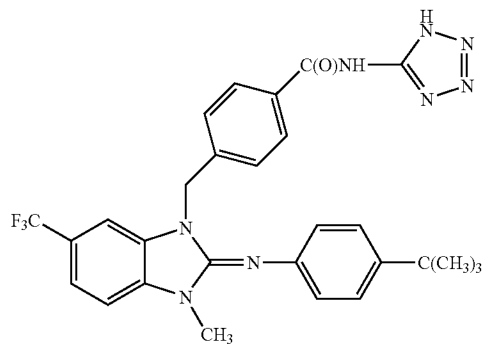

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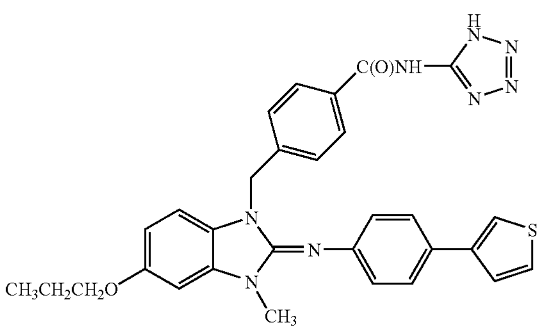


[0274] Pharmaceutically acceptable salts and solvates of the species noted above are also included.

[0275] The invention further includes a pharmaceutical composition which is comprised of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, in combination with a pharmaceutically acceptable carrier.

[0276] Also included is a method of treating type 2 diabetes mellitus in a mammalian patient in need of such treatment, comprising administering to said patient a compound of formula I in an amount that is effective to treat type 2 diabetes mellitus.

[0277] Also included is a method of preventing or delaying the onset of type 2 diabetes mellitus in a mammalian patient in need thereof, comprising administering to said patient a compound of formula I in an amount that is effective to prevent or delay the onset of type 2 diabetes mellitus.

[0278] Also included in the present invention is a method of treating hyperglycemia, diabetes or insulin resistance in a mammalian patient in need of such treatment which comprises administering to said patient an effective amount of a compound of formula I.

[0279] Also included in a method of treating, preventing or delaying the onset of diseases or conditions that are associated with type 2 diabetes mellitus. Examples include diseases and conditions selected from the group consisting of: dyslipidemias, (e.g., hyperlipidemia), such as elevated levels of cholesterol (hypercholesterolemia), triglycerides (hypertriglyceridemia) or low density lipoproteins (LDL) (high LDL levels), low levels of high density lipoprotein (HDL), microvascular or macrovascular changes and the sequellae of such conditions, such as coronary heart disease, stroke, peripheral vascular disease, hypertension, renal hypertension, nephropathy, neuropathy and retinopathy. The method entails administering to a type 2 diabetic patient, e.g., a human patient, an amount of a compound of formula I that is effective for treating, preventing or delaying the onset of such diseases or conditions.

[0280] Also included in the present invention is a method of treating atherosclerosis in a mammalian patient in need of such treatment, comprising administering to said patient a compound of formula I in an amount effective to treat atherosclerosis.

[0281] Also included in the present invention is a method of treating a condition selected from the group consisting of: (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) pancreatitis, (15) abdominal obesity, (16) neurodegenerative disease, (17) retinopathy, (18) nephropathy, (19) neuropathy, (20) Syndrome X, and other conditions and disorders where insulin resistance is a component, in a mammalina patient in need of such treatment, comprising administering to the patient a compound in accordance with formula I in an amount that is effective to treat said condition.

[0282] Also included in the present invention is a method of delaying the onset of a condition selected from the group consisting of (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high IDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) pancreatitis, (15) abdominal obesity, (16) neurodegenerative disease, (17) retinopathy, (18) nephropathy, (19) neuropathy, (20) Syndrome X, and other conditions and disorders where insulin resistance is a component in a mammalian patient in need of such treatment, comprising administering to the patient a compound of formula I in an amount that is effective to delay the onset of said condition.

[0283] Also included in the present invention is a method of reducing the risk of developing a condition selected from the group consisting of (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) pancreatitis, (15) abdominal obesity, (16) neurodegenerative disease, (17) retinopathy, (18) nephropathy, (19) neuropathy, (20) Syndrome X, and other conditions and disorders where insulin resistance is a component in a mammalian patient in need of such treatment, comprising administering to the patient a compound of formula I in an amount that is effective to reduce the risk of developing said condition.

Optical Isomers—Diastereomers—Geometric Isomers—Tautomers

[0284] Many of the compounds of formula I contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention includes all such isomeric forms of the compounds, in pure form as well as in mixtures.

[0285] Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

[0286] Some of the compounds described herein may exist with different points of attachment of hydrogen, referred to as tautomers. Such an example may be a ketone and its enol form known as keto-enol tautomers. The individual tautomers as well as mixture thereof are encompassed with compounds of Formula I.

Salts and Solvates

[0287] The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable substantially non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids, as well as salts that can be converted into pharmaceutically acceptable salts. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

[0288] When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

[0289] Solvates as used herein refers to the compound of formula I or a salt thereof, in association with a solvent, such as water. Representative examples include hydrates, hemihydrates, trihydrates and the like.

[0290] References to the compounds of Formula I include the pharmaceutically acceptable salts and solvates.

[0291] This invention relates to method of antagonizing or inhibiting the production or activity of glucagon, thereby reducing the rate of gluconeogenesis and glycogenolysis, and the concentration of glucose in plasma.

[0292] The compounds of formula I can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of disease states in mammals caused by elevated levels of glucose, comprised of combining the compound of formula I with the carrier materials to provide the medicament.

Dose Ranges

[0293] The prophylactic or therapeutic dose of a compound of formula I will, of course, vary with the nature of the condition to be treated, the particular compound selected and its route of administration. It will also vary according to the age, weight and response of the individual patient. In general, the daily dose range lie within the range of from about 0.001 mg to about 100 mg per kg body weight, preferably about 0.01 mg to about 50 mg per kg, and more preferably 0.1 to 10 mg per kg, in single or divided doses. It may be necessary to use dosages outside of these limits in some cases. The terms "effective amount""anti-diabetic effective amount" and the other terms appearing throughout the application addressing the amount of the compound to be used refer to the dosage ranges provided, taking into account any necessary variation outside of these ranges, as determined by the skilled physician.

[0294] Representative dosages for adults range from about 0.1 mg to about 1.0 g per day, preferably about 1 mg to about 200 mg, in single or divided doses.

[0295] When intravenous or or oral administration is employed, a representative dosage range is from about 0.001 mg to about 100 mg (preferably from 0.01 mg to about 10 mg) of a compound of Formula I per kg of body weight per day, and more preferably, about 0.1 mg to about 10 mg of a compound of Formula I per kg of body weight per day.

Pharmaceutical Compositions

[0296] As mentioned above, the pharmaceutical composition comprises a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof and a pharmaceutically acceptable carrier. The term "composition" encompasses a product comprising the active and inert ingredient(s), (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results, directly or indirectly, from the combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions between ingredients. Preferably the composition is comprised of a compound of formula I in an amount that is effective to treat, prevent or delay the onset of type 2 diabetes mellitus, in combination with the pharmaceutically acceptable carrier.

[0297] Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Examples of dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols and the like, with oral tablets being preferred. Thus, one aspect of the invention that is of interest is the use of a compound of formula I for preparing a pharmaceutical composition which is comprised of combining the compound of formula I with the carrier.

[0298] In preparing oral compositions, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquids, e.g., suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solids, e.g., powders, capsules and tablets, with the solid oral preparations being preferred. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit forms. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

[0299] In addition to the common dosage forms set out above, the compounds of Formula I may also be administered by controlled release means and/or delivery devices such as those described in U.S. Pat. Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719.

[0300] Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 1 mg to about 1 g of the active ingredient and each cachet or capsule contains from about 1 to about 500 mg of the active ingredient.

[0301] The following are examples of pharmaceutical dosage forms for the compounds of Formula I:

Injectable Suspension (I.M.)	mg/mL
Compound of Formula I	10
Methylcellulose	5.0
Tween 80	0.5
Benzyl alcohol	9.0
Benzalkonium chloride	1.0
Water for injection to make	1.0 mL

-continued

Tablet	mg/tablet
Compound of Formula I	25
Microcrystalline Cellulose	415
Povidone	14.0
Pregelatinized Starch	43.5
Magnesium Stearate	2.5
Total	500 mg
Capsule	**mg/capsule**
Compound of Formula I	25
Lactose Powder	573.5
Magnesium Stearate	1.5
Total	600 mg
Aerosol	**Per canister**
Compound of Formula I	24 mg
Lecithin, NF Liq. Conc.	1.2 mg
Trichlorofluoromethane, NF	4.025 g
Dichlorodifluoromethane, NF	12.15 g

Combination Therapy

[0302] Compounds of Formula I may be used in combination with other drugs that are used in the treatment/prevention/delaying the onset of type 2 diabetes mellitus, as well as the diseases and conditions associated with type 2 diabetes mellitus, for which compounds of Formula I are useful. Other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of Formula I is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of Formula I. Examples of other active ingredients that may be combined with a compound of Formula I, either administered separately or in the same pharmaceutical compositions, include, but are not limited to: (a) bis-guanides (e.g., buformin, metformin, phenformin), (b) PPAR agonists (e.g., troglitazone, pioglitazone, rosiglitazone), (c) insulin, (d) somatostatin, (e) α-glucosidase inhibitors (e.g., voglibose, miglitol, acarbose), (f) DP-IV inhibitors, (g) IXR modulators and (h) insulin secretagogues (e.g., acetohexamide, carbutamide, chlorpropamide, glibomuride, gliclazide, glimerpiride, glipizide, gliquidine, glisoxepid, glyburide, glyhexamide, glypinamide, phenbutamide, tolazamide, tolbutamide, tolcyclamide, nateglinide and repaglinide).

[0303] The weight ratio of the compound of the Formula I to the second active ingredient may be varied within wide limits and depends upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the Formula I is combined with a PPAR agonist the weight ratio of the compound of the Formula I to the PPAR agonist will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the Formula I and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

[0304] For combination products, the compound of formula I may be combined with any other active ingredients and then added to the carrier ingredients; alternatively the order of mixing may be varied.

[0305] Examples of pharmaceutical combination compositions include:

[0306] (1) a compound according to formula I,

[0307] (2) a compound selected from the group consisting of:

[0308] (a) DP-IV inhibitors;

[0309] (b) insulin sensitizers selected from the group consisting of (i) PPAR agonists and (ii) biguanides;

[0310] (c) insulin and insulin mimetics;

[0311] (d) sulfonylureas and other insulin secretagogues;

[0312] (e) α-glucosidase inhibitors;

[0313] (f) glucagon receptor antagonists;

[0314] (g) GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists;

[0315] (h) GIP, GIP mimetics, and GIP receptor agonists;

[0316] (i) PACAP, PACAP mimetics, and PACAP receptor 3 agonists;

[0317] (j) cholesterol lowering agents selected from the group consisting of (i) HMG-CoA reductase inhibitors, (ii) sequestrants, (iii) nicotinyl alcohol, nicotinic acid or a salt thereof, (iv) PPARα agonists, (v) PPARα/γ dual agonists, (vi) inhibitors of cholesterol absorption, (vii) acyl CoA:cholesterol acyltransferase inhibitors, (viii) anti-oxidants and (ix) LXR modulators;

[0318] (k) PPARδ agonists;

[0319] (l) antiobesity compounds;

[0320] (m) an ileal bile acid transporter inhibitor;

[0321] (n) anti-inflammatory agents other than glucocorticoids; and

[0322] (o) protein tyrosine phosphatase-1B (PTP-1B) inhibitors;

[0323] and

[0324] (3) a pharmaceutically acceptable carrier

[0325] In accordance with the methods described herein one method that is of interest relates to a method of treating a condition selected from the group consisting of (1) hyperglycemia, (2) low glucose tolerance, (3) insulin resistance, (4) obesity, (5) lipid disorders, (6) dyslipidemia, (7) hyperlipidemia, (8) hypertriglyceridemia, (9) hypercholesterolemia, (10) low HDL levels, (11) high LDL levels, (12) atherosclerosis and its sequelae, (13) vascular restenosis, (14) pancreatitis, (15) abdominal obesity, (16) neurodegenerative disease, (17) retinopathy, (18) nephropathy, (19) neuropathy, (20) Syndrome X, and other conditions and disorders where insulin resistance is a component, in a mammalian patient in need of such treatment, comprising administering to the patient an effective amount of a compound of formula I and a compound selected from the group consisting of:

[0326] (a) DP-IV inhibitors;

[0327] (b) insulin sensitizers selected from the group consisting of (i) PPAR agonists and (ii) biguanides;

[0328] (c) insulin and insulin mimetics;

[0329] (d) sulfonylureas and other insulin secretagogues;

[0330] (e) α-glucosidase inhibitors;

[0331] (f) glucagon receptor antagonists;

[0332] (g) GLP-1, GLP-1 mimetics, and GLP-1 receptor agonists;

[0333] (h) GIP,GEP mimetics, and GIP receptor agonists;

[0334] (i) PACAP, PACAP mimetics, and PACAP receptor 3 agonists;

[0335] (j) cholesterol lowering agents selected from the group consisting of (i) HMG-CoA reductase inhibitors, (ii) sequestrants, (iii) nicotinyl alcohol, nicotinic acid and salts thereof, (iv) PPARα agonists, (v) PPARα/γ dual agonists, (vi) inhibitors of cholesterol absorption, (vii) acyl CoA:cholesterol acyltransferase inhibitors, (viii) anti-oxidants and (ix) LXR modulators;

[0336] (k) PPARδ agonists;

[0337] (l) antiobesity compounds;

[0338] (m) an ileal bile acid transporter inhibitor

[0339] (n) anti-inflammatory agents excluding glucocorticoids; and

[0340] (o) protein tyrosine phosphatase-1B (PTP-1B) inhibitors, said compounds being administered to the patient in an amount that is effective to treat said condition.

[0341] More particularly, a method that is of interest relates to a method of treating a condition selected from the group consisting of-hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, hyperkriglyceridemia and dyslipidemia, in a mammalina patient in need of such treatment, comprising administering to the patient a therapeutically effective amount of a compound of formula I and an HMG-CoA reductase inhibitor.

[0342] Even more particularly, the method that is of interest comprises administering to the patient a therapeutically effective amount of a compound of formula I and an HMG-CoA reductase inhibitor wherein the MG-CoA reductase inhibitor is a statin, and even more particularly, the statin is selected from the group consisting of lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, itavastatin, ZD-4522 and rivastatin.

[0343] A different aspect of the invention relates to a method of reducing the risk of developing a condition selected from the group consisting of hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, hypertriglyceridemia and dyslipidemia, and the sequelae of such conditions comprising administering to a mammalian patient in need of such treatment a therapeutically effective amount of a compound of formula I and an HMG-CoA reductase inhibitor.

[0344] Another aspect of the invention relates to a method for delaying the onset or reducing the risk of developing atherosclerosis in a human patient in need of such treatment comprising administering to said patient an effective amount of a compound of formula I and an HMG-CoA reductase inhibitor. More particularly, the method comprises administering an effective amount of a compound of formula I and an HMG-CoA reductase inhibitor wherein the HMG-CoA reductase inhibitor is a statin. Even more particularly, the method comprises administering a compound of formula I and a statin selected from the group consisting of: lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, itavastatin, ZD4522 and rivastatin. Still more particularly, the method comprises administering a compound of formula I and the statin known as simvastatin.

[0345] Another aspect of the invention relates to a method of reducing the risk of developing a condition selected from the group consisting of hypercholesterolemia, atherosclerosis, low HDL levels, high LDL levels, hyperlipidemia, hypertriglyceridemia and dyslipidemia, and the sequelae of such conditions comprising administering to a mammalian patient in need of such treatment a therapeutically effective amount of a compound of formula I and a cholesterol absorption inhibitor. In particular, the method comprises administering an effective amount of a compound of formula I and the cholesterol absorption inhibitor known as ezetimibe.

[0346] More particularly, a method for delaying the onset or reducing the risk of developing atherosclerosis in a human patient in need of such treatment is described which comprises administering to said patient an effective amount of a compound of formula I and a cholesterol absorption inhibitor. More particularly, the method comprises administering a compound of formula I and the cholesterol absorption inhibitor known as ezetimibe.

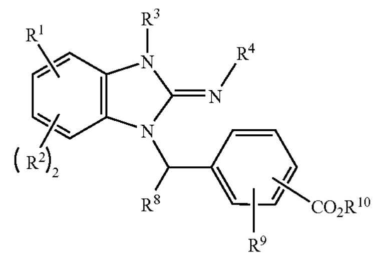
[0347] Throughout the instant application, the following abbreviations are used with the following meanings unless otherwise indicated:

Bu = butyl, t-Bu= t-butyl	Bn and Bnzl = benzyl
BOC, Boc = t-butyloxycarbonyl	CBZ, Cbz = Benzyloxycarbonyl
DCC = Dicyclohexylcarbodiimide	DCM = dichloromethane
DIEA = diisopropylethylamine	DMF = N,N-dimethylformamide
DMAP = 4-Dimethylaminopyridine	Et = ethyl
EtOAc = ethyl acetate	EtOH = ethanol
eq. = equivalent(s)	FAB-mass spectrum = Fast atom bombardment-mass spectroscopy
HOAc = acetic acid	
HOBT, HOBt = Hydroxybenztriazole	HPLC = High pressure liquid chromatography
Me = methyl	LAH = Lithium aluminum hydride
Ph = phenyl	PBS = phosphate buffer saline
THF = Tetrahydrofuran	TFA = Trifluoroacetic acid
C_6H_{11}= cyclohexyl	TMS = Trimethylsilane
iPr = isopropyl	Nme_2= dimethylamino
2,4-diClPh = 2,4-dichlorophenyl	2ClPh = 2-chlorophenyl
	Py, Pyr = pyridyl

[0348] Compounds of the present invention may be prepared according to the methodology outlined in the following general synthetic schemes.

[0349] In one embodiment of the present invention, the compounds (Ia) may be prepared from ester IIa (vide infra),

IIa

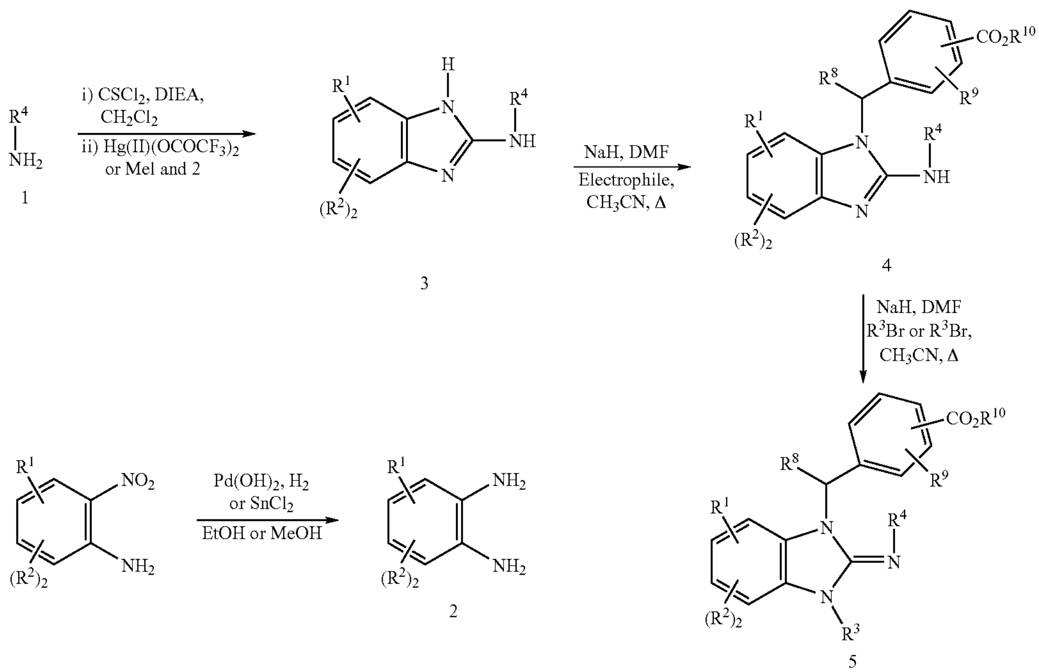


where R^1, R^2, R^3, R^4, R^8, and R^9 are as defined above and R^{10} represents an alkyl or aryl group.

[0350] Compounds IIa can be prepared using a variety of methods which will become apparent to those of ordinary skill from the teachings herein, one such route being illustrated in Scheme 1. Aniline 1 is treated with thiophosgene in the presence of a base such as diethylisopropylamine (DIEA) in a nonpolar aprotic solvent such as dichloromethane at temperatures of zero to 25° C. followed by direct addition of a 1,2-diaminobenzene 2 and either mercury (II) trifluoroacetate or methyl iodide (for example *J. Med. Chemi.,* 1985, 28, 1925 and *Synthesis,* 1974, 41). The reaction is stirred a further 30 min to 6 h before isolation of benzimnidazole 3 with an aqueous work-up. 1,2-Diaminobenzene analogs 2 are commercially available, or readily prepared by those skilled in the art by reduction of the corresponding 2-nitroaniline with, for example hydrogen and a palladium catalyst or stannous chloride. Either reaction is effected in an alcoholic solvent such as methanol or ethanol. In some instances, the isothiocyanates prepared in situ above are commercially available and can be used directly in the reaction.

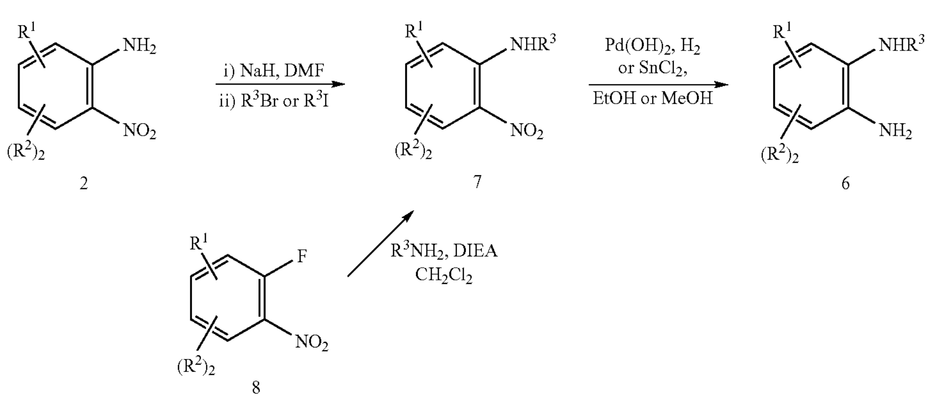
[0351] Benzimidazole 3 is converted to intermediate 4 by deprotonation with a base such as sodium hydride in a polar aprotic solvent such as dimethylformamide (DM) at 0-25° C. for 15 min to 2 h, followed by addition of a benzyl electrophile such as 4-carbomethoxy benzyl bromide. The reaction is stirred, with heating if necessary, for an additional 1-24 h to give intermediate 4. The alkylation can alternatively be achieved in the absence of base by stirring the electrophile with benzimidazole 3 in a polar aprotic solvent such DMF or acetonitrile at elevated temperatures for 6-24 h. At this point mixtures of isomers may be obtained, compounds can be separated by recrystallization, trituration, preparative thin layer chromatography, flash chromatography on silica gel as described by W. C. Still et al, *J. Org. Chem.,* 43, 2923, (1978), or HPLC. Compounds purified by HPLC may be isolated as the corresponding salt. Purification of intermediates is achieved in the same manner. The above reaction should be repeated on intermediate 4, using an electrophile such as methyl iodide to give the fully elaborated cyclic guanidine intermediate 5.

SCHEME 1



[0352] An alternate route to cyclic guanidine 5 is illustrated in Scheme 2 and 3. and goes via the N-alkylated 1,2-diaminobenzene 6. These are commercially available or readily prepared by those skilled in art. One such method involves alkylation of a 2-nitro aniline. This is effected by deprotonation with a base such as sodium hydride in a polar aprotic solvent such as dimethylformamide (DMF) at 0-25° C. for 15 min to 2 h, followed by addition of an electrophile such as an alkyl iodide, Scheme 2. The reaction is stirred for an additional 1-24 h to give intermediate 7, which can be reduced with, for example hydrogen and a palladium catalyst or stannous chloride in an alcoholic solvent. The alkylated 2-nitro aniline 7 can also be prepared by nucleophilic displacement of fluorine from a 2-fluoronitrobenzene 8 with an amine as described in *J. Org. Chem.,* 1999, 64, 3060. This is achieved in a solvent such as methylene chloride or DMF with a base such as DIEA, at temperatures of 25-80° C. for 1-6 h, Scheme 2. The diaminobenzene 6 can then be converted to the benzimidazole 9 using amine 1 in an identical fashion to that described above. Finally, reaction with an appropriate electrophile such as 4-carbomethoxy benzyl bromide gives intermediate 5, vide supra and illustrated in Scheme 3. The order of reaction with the two electrophiles may be reversed, such that intermediate 2 is first elaborated with the benzyl bromide to give, after reaction with amine 1 benzimidazole 4 which is converted to 5 as in Scheme 1.

SCHEME 2



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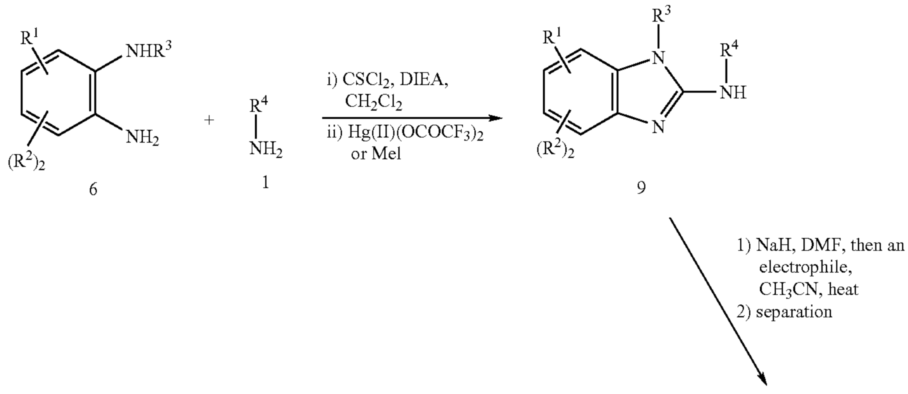
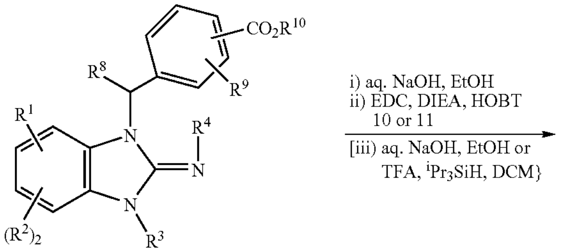
SCHEME 3



6 1 9 5

[0353] Preparation of the desired compounds Ia is then achieved by saponification of the ester 5 using a base such as aqueous lithium or sodium hydroxide in a polar solvent such as tetrahydrofuran, methanol, ethanol or a mixture of similar solvents, Scheme 4. Coupling of the acid with an amine, generally 5-aminotetrazole 10 or a beta alanine derivative 11 which may be substituted at the 2-position, is then achieved using 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC), 1-hydroxybenzotriazole (HOBt), and a base, generally diisopropylethylamine, in a solvent such as N,N-dimethylformamide (DMF) or methylene chloride for 3 to 48 hours at ambient temperature to yield the compounds Ia-10 and Ia-11. Other peptide coupling conditions may also be used. The product is purified from unwanted side products by recrystallization, trituration, preparative thin layer chromatography, flash chromatography on silica gel as described by W. C. Still et al, *J. Org. Chem.,* 43, 2923, (1978), or HPLC. Compounds purified by HPLC may be isolated as the corresponding salt. Purification of intermediates is achieved in the same manner. As will be understood by those skilled in the art, for the preparation of enantiomerically pure compounds, enantiomerically pure starting materials should be used.

SCHEME 4



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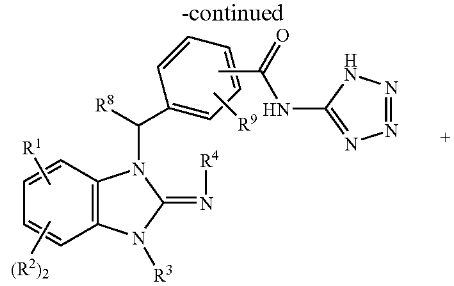
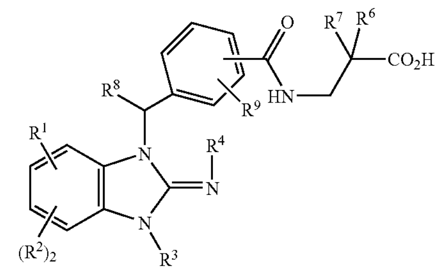
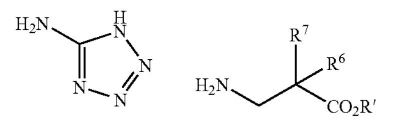


Ia-10



Ia-11

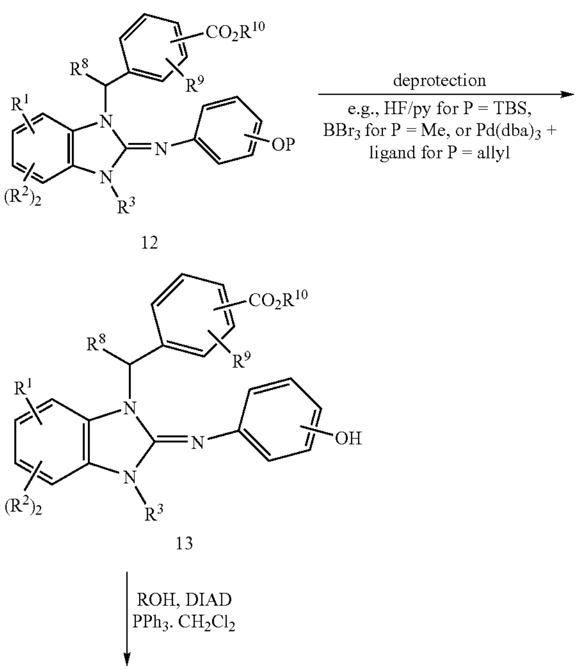


10 11

R′ = Me, Et, or ^{t}Bu

[0354] In some cases further modification of intermediates such as 5 can be undertaken in one of several different ways. These manipulations may include, but are not limited to substitution, reduction, oxidation, alkylation, acylation, and hydrolysis reactions, which are commonly known to those skilled in the art. One such modification, illustrated here when R^4 is a protected phenol as in 12, involves release of the alcohol and subsequent etherification. The hydroxyl group may be protected as a silyl ether, in which case a fluoride source, generally hydrofluoric acid or tetrabutylammonium fluoride is used for the reaction. Deprotection of a methoxy ether is routinely effected by treatment of the compound with boron tribromide in a solvent such as methylene chloride for a period of 1-16 h at ambient temperatures. Finally, if the alcohol is protected as an alkyl ether this is removed by treatment with dimethylbarbituric acid and a palladium catalyst, routinely tris(dibenzylideneacetone)dipalladium(0), with a ligand such as 1,4-bis-(diphenylphospino)butane in an aprotic solvent such as methylene chloride for 15 min to 2 h. See "Protective Groups in Organic Synthesis", Greene, published by Wiley and Sons.

SCHEME 5



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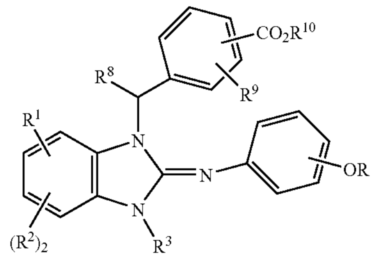

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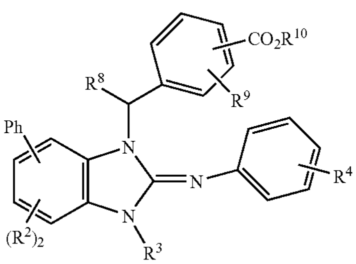
[0355] The free hydroxyl group may then be further modified to prepare ethers using an alcohol and coupling agent, such as diisopropylazodicarboxylate (DIAD), and triphenylphosphine in a non polar solvent such as methylene chloride at temperatures of 0 to 40° C. for 1 to 16 h, Scheme 5. Intermediates 13 and 14 can then be converted to the desired products as previously described, vide supra. Similar chemistry can be applied in the case when R^1 or R^2 are protected alcohols.

[0356] Other modifications, illustrated here when R^1 contains an aromatic bromide or iodide as in 15, Scheme 6, involve coupling reactions for example in a Suzuki type coupling where the halide is coupled with a boronic acid, exemplified here with phenyl boronic acid, using a palladium catalyst such as palladium acetate and tris-o-tolylphosphine or triphenyl phosphine. The solvent is generally DMF, toluene or ethanol, and cesium carbonate or aqueous sodium carbonate is also added to the reaction, which is performed at elevated temperatures for 12-24 h (see *Helv. Chim. Acta,* 1992, 75, 855). Alternatively bromide 15 can be coupled with an alkenyl stannane 17 (in which R'=alkyl) or alkyl zinc reagent 18 using a palladium catalyst such as triphenyl phosphine in a polar solvent such as THF or DMF at elevated temperatures (see *J. Org. Chem.,* 1998, 63, 3764). Coupling with an alcohol to provide ethers 21 is again achieved with a palladium catalyst, most usually palladium acetate and a phosphine ligand in the presence of a base such as cesium carbonate in a non polar aprotic solvent such as toluene at elevated temperatures (see *J. Am. Chem. Soc.,* 2001, 123, 10770).

SCHEME 6



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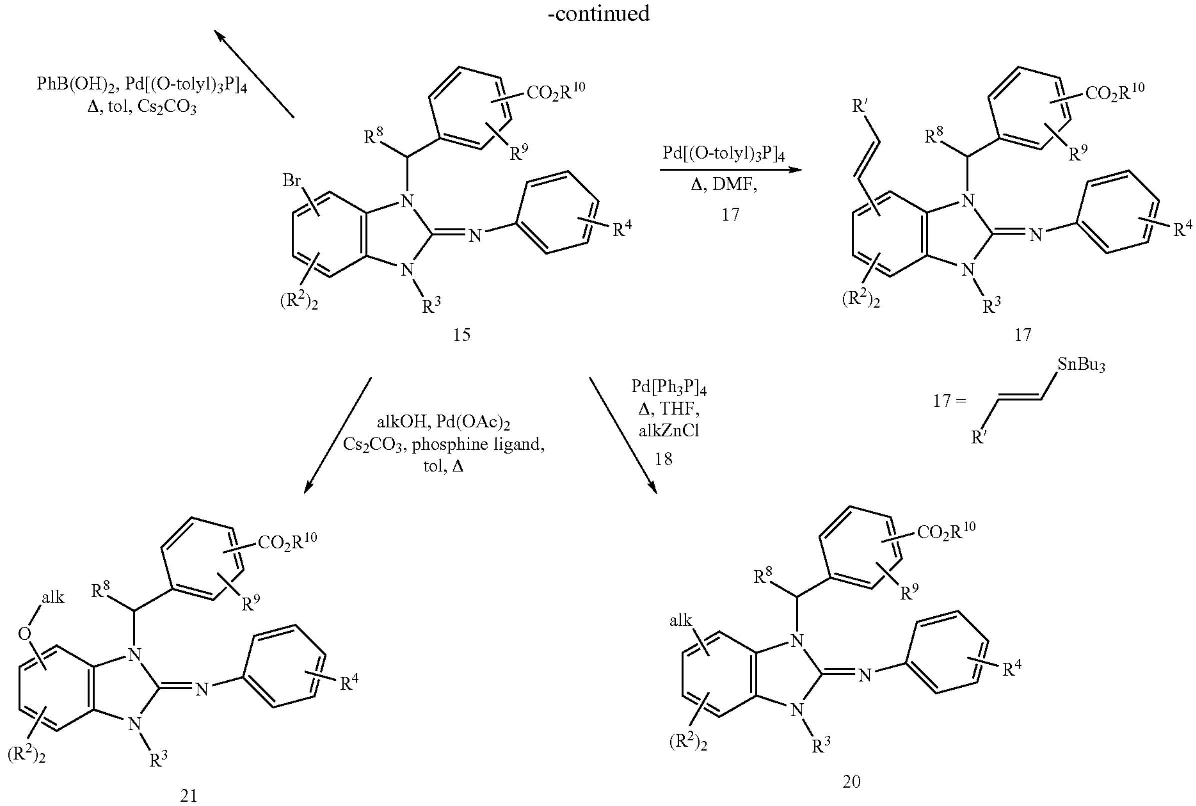


Similar chemistry can be applied in the case when R^2 or R^4 are aromatic bromides or iodides. Intermediates 16 and 19-21 can then be converted to the desired products as previously described, vide supra.

LC-MS Conditions:

[0357] Method A: column: Waters Xterra C18 (3.0×50 mm). Gradient: 10-98% MeCN (containing 0.05% TFA)/H_2O (containing 0.06% TFA) over 3.75 min@ 1 mL/min

[0358] Method B: column: MetaChem Polaris (4.6×50 mm). Gradient: 5-95% MeCN/H_2O, (both with 0.05% TFA) over 2.5 min@ 2.5 mL/min

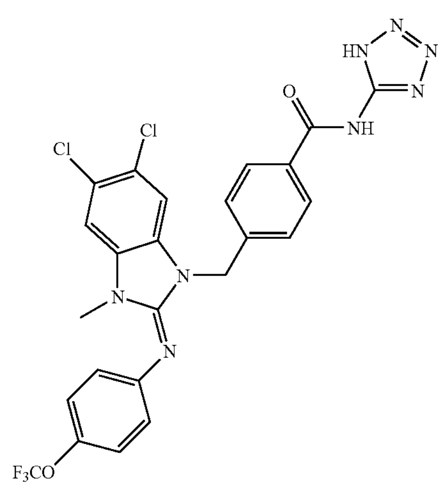
[0359] Method C: column: Waters Xterra C18 (3.0×50 mm). Gradient: 10-100% MeCN (containing 0.05% formic acid)/H_2O (containing 0.06% formic acid) over 3.75 min@ 1 mL/min

[0360] Preparative HPLC was performed on a YMC-Pack Pro C18 column (150×20 mm i.d.) at an initial flow rate of 4 mL/min for 1.35 min, followed by 20 mL/min for 10.6 min. The gradients employed during the faster part of the run are described, and all runs were followed with 100% organic at 20 mL/min for 0.5 min.

[0361] The following examples are provided so that the invention might be more fully understood. They should not be construed as limiting the invention in any way.

EXAMPLE 1

[0362]



Method 1

Step A. 4,5-dichloro-N-methyl-2-nitroaniline

[0363] To a solution of 4,5-dichloro-2-nitroaniline (10 mmol, 2.07 g) in DMF (10 mL) was added NaH (12 mmol, 480 mg of 60% suspension in mineral oil) (exothermic, gas evolution). After 15 min MeI (20 mmol, 1.2 mL) was added. The reaction mixture was allowed to stand at ambient temperature for 1 h, then poured into a solution of saturated $NaHCO_3$ and brine, affording the product as an orange precipitate, which was filtered, washed with water and dried in vacuo. ^{1}H NMR (500 MHz, d_6-DMSO) δ 8.27 (m, 1H), 8.22 (s, 1H), 7.25 (s, 1H), 2.96 (d, J=4.9 Hz, 3H).

Step B. 4,5-Dichloro-N-methylbenzene-1,2-diamine

[0364] The title compound of Example 1, Method 1, Step A (5 mmol, 1.1 g) and $SnCl_2.2H_2O$ (15 mmol, 3.4 g) were stirred in 40 mL of DMF at 40° C. for 16 hr. The reaction mixture was diluted with CH_2Cl_2, poured into saturated $NaHCO_3$ and stirred for 1 h. The resulting slurry was filtered over celite, and the filter cake was washed with CH_2Cl_2. The organic phase was collected, dried with Na_2SO_4 and concentrated in vacuo to afford a brown oil. Flash chromatography on silica eluting with 20% EtOAc in hexanes provided the product as a purple solid. LC-MS (ESI, Method B): 1.58 min, m/z 191.1 (M+1).

Step C. 5,6-Dichloro-1-methyl-N-[4-(trifluoromethoxy)phenyl]-1H-benzimidazol-2-amine

[0365] A solution of the title compound in Example 1, Method 1, Step B (0.6 mmol, 114 mg) and 4-trifluoromethoxyphenyl isothiocyanate (0.6 mmol, 97 μL) was heated in CH_2Cl_2 (1 mL) at 40° C. for 1 h, then allowed to stand at ambient temperature for 16 h. DIEA (1.2 mmol, 209 μL) and MeI (0.9 mmol, 75 μL) were added to the reaction, and the resultant mixture was heated at 40° C. for 5 h, then purified directly by flash chromatography on silica eluting with a step gradient of 20-25% EtOAc in hexanes. LC-MS (ESI, Method B): 1.94 min, m/z 376.1 (M+1).

Step D. Methyl 4-[(5,6-dichloro-3-methyl-2-{[4-(trifluoromethoxy)phenyl]imino}-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzoate

[0366] To the title compound of Example 1, Method 1, Step C (0.38 mmol, 144 mg) in DMF (1.2 mL) was added NaH (0.46 mmol, 18 mg of a 60% suspension in mineral oil). After 10 min methyl-4-(bromomethyl)benzoate (0.46 mmol, 105 mg) was added and the reaction mixture was left at ambient temperature for 16 h. The reaction mixture was partitioned between CH_2Cl_2 and $NaHCO_3$. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica eluting with 20% EtOAc in hexanes afforded the product. ^{1}H NMR (500 MHz, d_6-DMSO) δ 7.89 (d, J=8 Hz, 2H), 7.45 (s, 1H), 7.37 (s, 1H), 7.29 (d, J=8 Hz, 2H), 7.12 (d, J=8 Hz, 2H), 6.86 (m, 2H), 5.13 (s, 2H), 3.84 (s, 3H), 3.14 (s, 3H). LC-MS (ESI, Method B): 2.10 min, m/z 524.0 (M+1).

Step E. 4-[(5,6-Dichloro-3-methyl-2-{[4-(trifluoromethoxy)phenyl]imino}-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzamide

[0367] To the title compound of Example 1, Method 1, Step D (0.17 mmol, 87 mg) in dioxane (1.6 mL) was added a solution of LiOH (0.8 mmol, 20 mg) in H_2O (0.8 mL). The reaction was stirred at 45° C. for 2 h. The product was partitioned between EtOAc and pH 7 phosphate buffer. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure to provide a yellow foamy solid. To a portion of the solid (0.12 mmol, 61 mg) was added a solution of 1H-tetraazol-5-amine monohydrate (0.36 mmol, 37 mg), HOBt (0.24 mmol, 37 mg), EDC (0.24 mmol, 46 mg) and DIEA (0.36 mmol, 63 μL) in DMF (1 mL). The reaction mixture was allowed to stand at ambient temperature for 16 h, then concentrated under reduced pressure. The residue was taken up in 2:1 dioxane/H_2O, acidified with TFA, and purified by reverse-phase chromatography (20-60% MeCN in H_2O, both containing 0.1% TFA). Lyophilization afforded the title compound as a white solid. ^{1}H NMR (500 MHz, d_6-DMSO+Et_3N): δ 7.90 (d, J=8 Hz, 1H), 7.44 (s, 1H), 7.39 (s, 1H), 7.25 (d, J=8 Hz), 2H), 7.15 (d, J=8 Hz, 2H), 6.89 (m, 2H), 5.11 (s, 2H), 3.15 (s, 3H). LC-MS (ESI, Method A): 2.86 min, m/z 577.2 (M+1).

Method 2.

Step A. 5,6-Dichloro-N-[4-(trifluoromethoxy)phenyl]-1H-benzimidazol-2-amine

[0368] A solution of 4,5-dichloro-1,2-phenylenediamine (2 mmol, 354 mg) and 4-trifluoromethoxyphenyl isothiocyanate (2 mmol, 325 μL) in CH_2Cl_2 (3 mL) was heated at 40° C. for 4 h. MeI (2.2 mmol, 137 μL) and DIEA (2.0 mmol, 348 μL) were added, and the reaction was brought to 40° C. for 24 h. The reaction mixture was partitioned between CH_2Cl_2 and brine. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. Chromatography on silica eluting with 20-40% EtOAc in hexanes provided the product as a tan solid. ^{1}H NMR (500 MHz, d_6-DMSO) δ 11.2 (br s, 1H), 9.91 (s, 1H), 7.84 (m, 2H), 7.52 (br s, 1H), 7.34 (d, J=9 Hz, 2H). LC-MS (ESI, Method A): 2.96 min, m/z 362.1 (M+1).

Step B. Methyl 4-[(5,6-dichloro-2-{[4-(trifluoromethoxy)phenyl]imino}-1H-benzimid-azol-1-yl)methyl]benzoate

[0369] To the title compound of Example 1, Method 2, Step A (0.36 mmol, 130 mg) in DMF (2.5 mL) was added NaH (0.43 mmol, 17 mg of 60% suspension in mineral oil). After 10 min methyl-4-(bromomethyl)benzoate (0.36 mmol, 82 mg) was added and the reaction mixture was left a ambient temperature for 1 h. Aqueous workup with CH_2Cl_2 and brine, followed by flash chromatography on silica eluting with 20% and 30% EtOAc in hexanes provided the product. ^{1}H NMR (500 Mz, d_6-DMSO) δ 9.59 (br s, 1H), 7.96 (d, J=9 Hz, 2H), 7.93 (d, J=8 Hz, 2H), 7.66 (s, 1H), 7.56 (s, 1H), 7.35 (d, J=9 Hz, 2H), 7.27 (d, J=8 Hz, 2H), 5.70 (s, 2H), 3.83 (s, 3H). LC-MS (ESI, Method B): 2.30 min, m/z 510.1 (M+1).

Step C. Methyl-4-[(5,6-Dichloro-3-methyl-2-{[4-(trifluoromethoxy)phenyl]imino}-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzoate

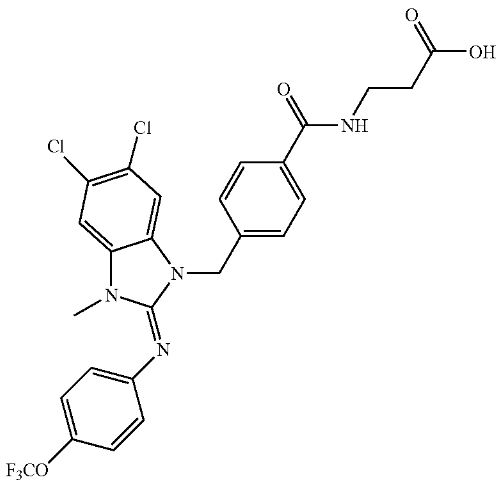
[0370] To a solution of the title compound of Example 1, Method 2, Step B (0.27 mmol, 138 mg) in DMF (1.5 mL) was added NaH (0.32 mmol, 13 mg of 60% suspension in mineral oil). After 5 min MeI (0.54 mmol, 34 μL) was added. After 2 h the reaction mixture was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was dried with $MgSO_4$ and concentrated in vacuo to afford the desired product [LC-MS (ESI, Method B): 2.13 min, m/z 524.1 (M+1)] and 2-N-methylbenzimidazole regioisomer [LC-MS (ESI, Method B): 2.32 min, m/z 524.1 (M+1)] in a ca. 2:1 ratio, which was taken on directly.

Step D. 4-[(5,6-Dichloro-3-methyl-2-{[4-(trifluoromethoxy)phenyl]imino}-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzamide

[0371] The product of Example 1, Method 2, Step C was dissolved in 1.6 mL of dioxane and a solution of LiOH (1.1 mmol, 26 mg) in 0.8 mL of H_2O was added. The reaction was stirred at 45° C. for 2 h, then partitioned between EtOAc and pH 7 phosphate buffer. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure to afford the product as an orange foam. To a portion of the solid containing the two N-methyl regioisomers (0.18 mmol, 93 mg) was added a solution of 1H-tetraazol-5-amine monohydrate (0.5 mmol, 48 mg), HOBt (0.3 mmol, 47 mg), EDC (0.3 mmol, 59 mg) and DIEA (0.5 mmol, 82 μL) in DMF (1.5 mL). The reaction mixture was brought to 40° C. for 1 h, then concentrated under reduced pressure. The residue was taken up in ca. 2:1 dioxane/H_2O, acidified with TFA, and purified by reverse-phase chromatography (20-60% MeCN/H_2O, both containing 0.1% TFA). Lyophilization afforded the title compound as a white solid. Spectroscopic data were identical with that obtained above.

EXAMPLE 2

[0372]

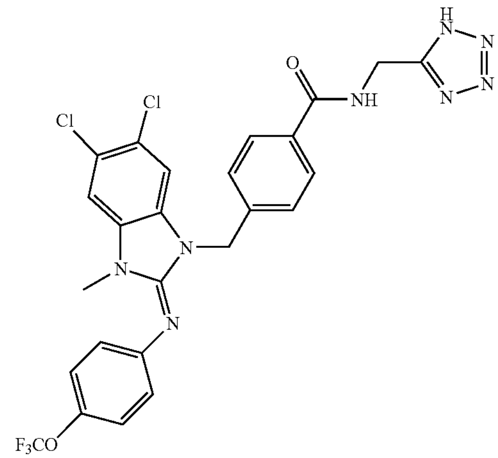


N-{4-[(5,6-Dichloro-3-methyl-2-{[4-(trifluoromethoxy)phenyl]imino}-2,3-dihydro-1H-benzimidazol-1-yl)methyl]benzoyl}-β-alanine

[0373] To the title compound of Example 1, Method 1, Step E (0.04 mmol, 20 mg) was added a solution of the hydrochloride salt of β-alanine tert-butyl ester (0.08 mmol, 15 mg), HOBt (0.0.08 mmol, 12 mg), EDC (0.08 mmol, 15 mg) and DIEA (0.12 mmol, 21 μL) in DMF (0.5 mL). The reaction mixture was allowed to stand at ambient temperature for 16 h, and then partitioned between EtOAc/H_2O. The organic phase was dried with $MgSO_4$ and the solvent was removed under reduced pressure. To the residue was added 1.2 mL of 2:30:68 H_2O/TFA/CH_2Cl_2. The resultant solution was stirred for 1 h and concentrated under reduced pressure. Reverse-phase chromatography (20-60% MeCN/H_2O, both containing 0.1% TFA), followed by lyophilization, afforded the product as a white solid. ^1H NMR (500 MHz, d_6-DMSO) δ 8.54 (t, J=5 Hz, 1H), 8.09 (s, 1H), 7.89 (s, 1H), 7.77 (d, J=8 Hz, 2H), 7.34 (d, J=9 Hz, 2H), 726 (d, J=9 Hz, 2H), 7.24 (d, J=8 Hz, 2H), 5.43 s, 2H), 3.42-3.47 (overlapping s, m, 5H), 2.50 (t, J=7 Hz, 2H). LC-MS (ESI, Method A): 2.78 min m/z 581.1 (M+1).

EXAMPLE 3

[0374]

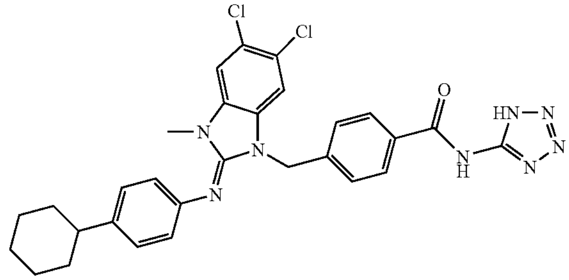


4-[(5,6-Dichloro-3-methyl-2-{[4-(trifluoromethoxy)phenyl]imino}-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-(1H-tetrazol-5-ylmethyl)benzamide

[0375] To the title compound of Example 1, Method 2, Step C (0.03 mmol, 15 mg) was added a solution of the hydrochloride salt of 2-aminomethyltetrazole (0.06 mmol, 8 mg), HOBt (0.06 mmol, 9 mg), EDC (0.06 mmol, 12 mg) and DIEA (0.09 mmol, 16 μL) in DMF (0.7 mL). The reaction mixture was brought to 40° C. for 2 h, then allowed to stand at ambient temperature for 16 h, and concentrated in vacuo. Purification by reverse-phase chromatography (20-60% MeCN/H_2O, both containing 0.1% TFA), followed by lyophilization, afforded the product as a white solid. ^1H NMR (500 MHz, d_6-DMSO) δ 9.23 (t, 5.6 Hz, 1H), 7.83 (d, J=8.5 Hz, 2H), 7.58-7.80 (overlapping br s, 2H), 7.22-7.34 (overlapping m, 4H), 7.04-7.20 (unres. m, 2H), 5.32 (br s, 2H), 4.75 (d, J=5.8 Hz, 2H). LC-MS (ESI, Method A): 3.02 min, m/z 591.1 (M+1).

EXAMPLE 4

[0376]



Step A. 5,6-Dichloro-N-[4-(cyclohexyl)phenyl]-1H-benzimidazol-2-amine

[0377] To a stirring solution of 4-cyclohexylaniline (10 mmol, 1.75 g) and DIEA (21 mmol, 3.65 mL) in CH_2Cl_2 (10 mL) at 0° C. was added thiophosgene (10 mmol, 700 μL) dropwise. The solution was allowed to reach ambient temperature for 1 h, and 4,5-dichloro-1,2-phenylenediamine (10.5 mmol, 1.86 g) was added. The reaction mixture was heated to reflux for 2 h, then concentrated in vacuo. The residue was taken up in a solution of EtOH (5 mL) and MeI (20 mmol, 1.25 muL), heated at 40° C. for 16 h, and concentrated in vacuo. Flash chromatography on silica eluting with 18-25% EtOAc in hexanes afforded the product as a red solid. LC-MS (ESI, Method C): 3.47 min, m/z 360.2 (M+1).

Step B. Methyl 4-[(5,6-dichloro-2-{[4-(cyclohexyl)phenyl]amino}-1H-benzimidazol-1-yl)methyl]benzoate

[0378] To the title compound of Example 4, Step A (1.1 mmol, 400 mg) in DMF (2 mL) was added NaH (1.2 mmol, 49 mg of 60% suspension in mineral oil). After 25 min methyl-4-(bromomethyl)benzoate (1.2 mmol, 280 mg) was added and the reaction mixture was allowed to stand at ambient temperature for 30 min. The reaction was diluted with saturated NH_4Cl (5 mL), and the crude product was extracted into EtOAc. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica eluting with 15% EtOAc in hexanes afforded the product as a yellow solid. LC-MS (ESI, Method C): 4.44 min, m/z 508.1 (M+1).

Step C. Methyl 4-[(5,6-dichloro-3-methyl-2-{[4-(cyclohexyl)phenyl]imino}-2,3-dihydro-1H-benzimidazol-1-yl-)methyl]-N-1H-tetrazol-5-ylbenzoate

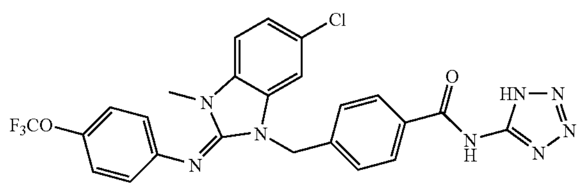
[0379] To a solution of the title compound of Example 4, Step B (0.38 mmol, 190 mg) in DMF (2 mL) was added NaH (0.56 mmol, 23 mg of 60% suspension in mineral oil). The reaction mixture was stirred for 20 min, and MeI (0.56 mmol, 35 μL) was added. After 1 h the reaction was quenched with saturated NH_4Cl and the crude product was extracted into EtOAc. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica eluting with 10-15% EtOAc in hexanes afforded the product as a beige foam. LC-MS (ESI, Method C): 4.64 min, m/z 522.2 (M+1).

Step D. 4-[(5,6-Dichloro-3-methyl-2-{[4-(cyclohexyl)phenyl]imino}-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzamide

[0380] To the title compound of Example 4, Step C (0.15 mmol, 79 mg) in dioxane (1.8 mL), was added a solution of LiOH (1.5 mmol, 36 mg) in H_2O (1 mnL). The resulting solution was stirred at ambient temperature for 16 h. The reaction mixture was concentrated in vacuo to remove dioxane, and then diluted with H_2O (3 mL) and neutralized with 2 N HCl. The resulting precipitate was filtered, washed with water and dried in vacuo to afford a white solid. A portion of the solid (0.07 mmol, 35 mg) was taken up in a solution of 1H-tetraazol-5-amine monohydrate (0.34 mmol, 35 mg), EDC (0.31 mmol, 60 mg), HOBt (0.17 mmol, 26 mg) and DIEA (0.35 mmol, 60 μL) in DMF (1 mL), and heated for 1 hr at 40 ° C. Purification by reverse-phase chromatography eluting with a gradient of 20-60% MeCN/H_2O, both containing 0.1% TFA, followed by lyophilization afforded the product as a white solid. ^{1}H NMR (500 MHz, CD_3OD), δ (ppm): 8.02 (d, J=8.5 Hz, 2H), 8.00 (s, 1H), 7.80 (s, 1H), 7.26 (d, J=6.1 Hz, 2H), 7.24 (d, J=6.4 Hz, 2H), 7.16 (d, J=8.7 Hz, 2H), 5.46 (s, 2H), 3.66 (s, 3H), 2.55 (m, 1H), 1.86 (m, 4H), 1.76 (m, 1H), 1.44 (m, 4H), 1.30 (m, 1H). LC-MS (ESI, Method C): 2.90 min, m/z 575.2 (M+1).

EXAMPLE 5

[0381]



Step A. 4-chloro-N-methyl-2-nitroaniline

[0382] To a solution of 4-chloro-2-nitroaniline (10 mmol, 1.73 g) in DMF (10 mL) was added portionwise NaH (12 mmol, 480 mg of a 60% suspension in mineral oil) (exothermic, gas evolution). After 10 min MeI (20 mmol, 1.2 mL) was added to the reaction mixture. After 1 h the reaction mixture was poured into aqueous $NaHCO_3$ and brine to afford the product as an orange precipitate, which was filtered, washed with water and dried in vacuo. H^1 NMR (500 MHz, d_6-DMSO): δ 8.22 (m, 1H), 8.02 (d, J=2.5 Hz, 1H), 7.56 (dd, J=9.1 Hz, 2.5 Hz, 1H), 7.02 (d, J=9.4 Hz, 1H), 2.94 (d, J=5.0 Hz, 3H).

Step B. 4-Chloro-1-N-methylbenzene-1,2-diamine

[0383] To the title compound in Example 5, Step A (5 mmol, 933 mg) in DMF (10 mL) was added SnCl2.2H_2O (15 mmol, 3.38 g). The reaction mixture was stirred at 40° C. for 16 h, then poured into EtOAc and saturated $NaHCO_3$, which resulted in formation of a yellow precipitate. The slurry was filtered through celite, the filter cake was washed with water and EtOAc, and the combined organic phase was dried with Na_2SO_4 and concentrated in vacuo to provide an orange oil. Purification by flash chromatography on silica eluting with 25% EtOAc in hexanes afforded the product as an amber solid. H^1 NMR (500 MHz, d_6-DMSO): δ 6.53 (d, J=2.6 Hz, 1H), 6.48 (dd, J=8.5 Hz, 2.5 Hz, 1H), 6.30 (d, J=8.5 Hz, 1H), 4.74 (br s, 3H), 2.67 (s, 3H). LC-MS (ESI, Method B): 1.16 min, m/z 157.1 (M+1).

Step C. 5-Chloro-1-methyl-N-[4-(trifluoromethoxy)phenyl]-1H-benzimidazol-2-amine

[0384] To a solution of the title compound in Example 5, Step B (0.3 mmol, 47 mg) in CH_2Cl_2 (0.5 mL) was added 4-trifluoromethoxyphenyl isothiocyanate (0.3 mmol, 49 μL). After 1 h MeI (0.5 mmol, 53 μL) was added. The reaction mixture was heated at 40° C. for 1 h, then allowed to stand at ambient temperature for 16 h. The reaction mixture was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was dried with Na_2SO_4 and concentrated in vacuo to afford a white solid. The product was isolated by flash chromatography on silica eluting with 25% EtOAc in hexanes. LC-MS (ESI, Method B): 1.67 min, m/z 342.1 (M+1).

Step D. Methyl 4-[(6-chloro-3-methyl-2-{[4-(trifluoromethoxy)phenyl]imino}-2,3-dihydro-1H-benzimidazol-1-yl)methyl]benzoate

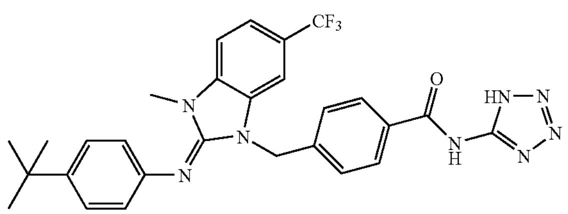
[0385] To the title compound of Example 5, Step C (0.13 mmol, 44 mg) in DMF (0.4 mL) was added NaH (0.15 mmol, 6 mg of 60% suspension in mineral oil). After 10 min methyl-4-(bromomethyl)benzoate (0.17 mmol, 39 mg) was added and the reaction mixture was allowed to stand at ambient temperature for 1 h. Aqueous workup with CH_2Cl_2/saturated $NaHCO_3$, followed by flash chromatography on silica eluting with 12% EtOAc in hexanes provided the product [LC-MS (ESI, Method C) 2.94 min, m/z 490.0 (M+1)], and the 2-N-benzyl regioisomer [LC-MS (ESI, Method C) 4.16 min, m/z 490.1 (M+1)], in a ca. 1:2 ratio.

Step E. 4-[(6-Chloro-3-methyl-2-{[4-(trifluoromethoxy)phenyl]imino}-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzamide

[0386] To the product of Example 5, Step D (0.11 mmol, 52 mg) in dioxane (1 mL), was added a solution of LiOH (1 mmol, 24 mg) in H_2O (0.5 mL). The resulting solution was stirred at 40° C. for 1 h, and partitioned into EtOAc/brine buffered to pH 7. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. To the residue was added a solution of 1H-tetraazol-5-amine monohydrate (0.2 mmol, 21 mg), EDC (0.2 mmol, 38 mg), HOBt (0.2 mmol, 31 mg) and DIEA (0.3 mmol, 52 μL) in DMF (1 mL). The reaction mixture was heated for 2 h at 40° C., Reverse-phase chromatography (20-60% MeCN/H_2O, both containing 0.1% TFA), followed by lyophilization, afforded the product as a white solid. ^{1}H NMR (500 MHz, d_6-DMSO+NH3): δ 7.97 (d, J=7.4 Hz, 2H), 7.33 (d, J=8.0 Hz), 7.19 (d, J=2.1 Hz, 1H), 7.08-7.15 (overlapping m, 3H), 7.05 (dd, J=8.5 Hz, 2.0 Hz, 1H), 6.88 (m, 2H), 6.53 (s, 1H), 5.14 (s, 2H), 3.13 (s, 3H). LC-MS (ESI, Method C) 2.48 min, m/z 543.1 (M+1).

EXAMPLE 6

[0387]



Step A. N-Methyl-2-nitro-4-(trifluoromethyl)aniline

[0388] To a solution of 2-nitro-4-trifluoromethylaniline (200 mmol, 41.2 g) in DMF (200 mL) cooled to 0° C. was added portionwise NaH (210 mmol, 8.4 g of a 60% suspension in mineral oil) (exothermic, gas evolution). The reaction was allowed to reach ambient temperature for 45 min, then cooled back to 0° C. MeI (220 mmol, 13.7 mL) was added via syringe (exothermic) and the resulting slurry was stirred for 2 h. The reaction mixture was poured into a 1:1 mixture of saturated NaHCOand brine (**[text missing or illegible when filed]**) to provide the product as a bright orange precipitate, which was filtered, washed with water and dried in vacuo. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 8.52 (d, J=1.2 H, 1H), 8.31 (br s, 1H), 7.70 (d, J=8.9 Hz, 1H), 6.98 (d, J=9.2 Hz, 1H), 3.13 (d, J=5.3 Hz, 3H). LC-MS (ESI, Method C): 3.34 min, m/z 221.1 (M+1).

Step B. N^1-methyl-4-(trifluoromethyl)benzene-1,2-diamine

[0389] The title compound of Example 6, Step A (150 mmol, 33 g) and Pearlman's catalyst (ca. 400 mg) were agitated in MeOH (200 mL) under H_2 (40 psi, Parr shaker) for 4 h. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo. Flash chromatography on silica eluting with 20-25% EtOAc in hexanes afforded the product as a light orange solid. ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.17 (1H, d, J=8.3 Hz), 6.97 (1H, d, J=1.9 Hz), 6.68 (1H, d, J=8.2 Hz), 3.78 (1H, bs), 3.38 (2H, bs), 2.94 (3H, s). LC-MS (ESI, Method C): 2.71, m/z 191.1 (M+1).

Step C. N-(4-tert-butylphenyl)-1-methyl-5-(trifluoromethyl)-1H-benzimidazol-2-amine

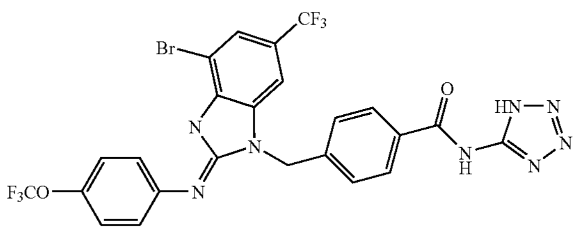
[0390] To a stirring solution of 4-t-butylaniline (1.3 mmol, 189 mg) and DIEA (2.53 mmol, 441 μL) in DCM (3 mL) at 0° C. was added dropwise thiophosgene (1.3 mmol, 91 μL). After 10 min the title compound of Example 6, Step B (10.5 mmol, 1.86 g) was added, and the reaction mixture was brought to 40° C. for 2 h. $Hg(O_2CCF_3)_2$ (2.5 mmol, 1 g) and DIEA (1.3 mmol, 220 μL) were added and the reaction was heated at 40° C. for 16 h. The reaction was poured into DCM and brine containing Na_2S, and the resulting slurry was filtered through celite. The organic phase was collected and dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography on silica eluting with 25% EtOAc in hexanes afforded the product as a yellow solid. LC-MS (ESI, Method B): 1.81 min, m/z 348.3 (M+1).

Step D. 4-[(2-{[4-(tert-butyl)phenyl]imino}-3-methyl-6-trifluoromethyl-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzamide

[0391] To the title compound of Example 6, Step C (0.2 mmol, 70 mg) in DMF (1.5 mL) was added NaH (0.4 mmol, 16 mg of 60% suspension in mineral oil). After 20 min methyl-4-(bromomethyl)benzoate (0.22 mmol, 51 mg) was added. The reaction mixture was allowed to stand at ambient temperature for 30 min, then concentrated in vacuo. The residue was taken up in dioxane (2 mL), and a solution of LiOH (2 mmol, 48 mg) in H_2O (1 mL) was added. The reaction mixture was stirred at 40° C. for 1 h, diluted with H_2O, and neutralized with 2 N HCl. The crude product was extracted with EtOAc, which was dried with $MgSO_4$ and concentrated in vacuo to afford a brown solid. The solid was taken up in a solution of 1H-tetraazol-5-amine monohydrate (1 mmol, 103 mg), EDC (0.8 mmol, 155 mg), HOBt (0.6 mmol, 92 mg) and DIEA (1 mmol, 175 μL) in DMF (1.5 mL) and heated for 3 h at 40° C. Reverse-phase chromatography (20-60% MeCN in H_2O, both containing 0.1% TFA) and lyophilization afforded the product as a white solid. ^{1}H NMR (500 MHz, CD_3OD), δ (ppm): 8.02 (d, J=8.4 Hz, 2H), 7.91-7.89 (m, 2H), 7.86 (d, J=8.7 Hz, 1H), 7.44 (d, J=8.7 Hz, 2H), 7.26 (d, J=8.5 Hz, 2H), 7.21 (d, J=8.7 Hz, 2H), 5.56 (s, 2H), 3.74 (s, 3H), 1.34 (s, 9H). LC-MS (ESI, Method B): 2.04 min, m/z 549.4 (M+1).

EXAMPLE 7

[0392]



Step A. 2-Bromo-N-methyl-6-nitro-4-(trifluoromethyl)aniline

[0393] To a solution of 4-amino-3-bromo-5-nitrobenzotrifluoride (5.25 g, 18.4 mmol) in DMF (40 mL) was added NaH (883 mg, 60% suspension in mineral oil, 22.1 mmol). After 30 min MeI (1.38 mL, 22.1 mmol) was added. The reaction mixture was allowed to stand at room temperature for 1 h, then was poured into a solution of saturated aqueous $NaHCO_3$ and brine. The resulting suspension was extracted twice with CH_2Cl_2, and the combined extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography (5% EtOAc in hexanes, then 8% EtOAc in hexanes) provided the title compound as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 7.86 (d, J=2.0 Hz, 1H), 6.47 (br s, 1H), 3.07 (d, J=5.5 Hz, 3H).

Step B. 2-Bromo-N^1-methyl-4-(trifluoromethyl)benzene-1,2-diamine

[0394] To a solution of the title compound in Example 7, Step A (5.78 g, 19.3 mmol) in DMF (40 mL) and H_2O (4 mL) was added $SnCl_2.2H_2O$ (14.6 g, 77.3), and the mixture was stirred at 40° C. for 16 h. The reaction mixture was then slowly poured into saturated aq. $NaHCO_3$ (exothermic) and CH_2Cl_2. The resulting slurry was filtered through Celite, and the filter cake was rinsed with CH_2Cl_2. The organic phase was collected, dried over Na_2SO_4, and concentrated in vacuo to give a red oil. Purification by flash chromatography (10% EtOAc in hexanes) afforded the product as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, J=1.5 Hz, 1H), 6.85 (d, J=1.5 Hz, 1H), 4.12 (br s, 2H), 3.44 (br s, 1H), 2.71 (s, 3H).

Step C. 7-Bromo-1-methyl-N-[4-(trifluoromethoxy)phenyl]-5-(trifluoromethyl)-1H-benzimidazol-2-amine

[0395] To a solution of the title compound in Example 7, Step B (250 mg, 0.93 mmol) in CH_2Cl_2 (3 mL) was added 4-trifluoromethoxyphenyl isothiocyanate (218 μL, 1.34 mmol), and the mixture was stirred at 40° C. After 1 h, the reaction mixture was allowed to cool to ambient temperature. DMF (3 mL) was added, followed by mercury trifluoroacetate (646 mg, 1.51 mmol), and the mixture was stirred at 40° C. for 12 h. The mixture was then poured into EtOAc/saturated aq. Na_2S, and the resulting black slurry was filtered through Celite. The organic phase was collected, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography (10% EtOAc/hexanes then 20% EtOAc/hexanes) provided the title compound as a white solid: ^{1}H NMR (500 MHz, CD_3OD) δ 7.71 (d, J=9.0 Hz, 2H), 7.63 (s, 1H), 7.52 (s, 1H), 7.29 (d, J=9.0 Hz, 2H), 4.08 (s, 3H). LC-MS (ESI, Method B) 2.04 min, m/z 455.9 (M+3).

Step D. Methyl 4-[(4-bromo-6-trifluoromethyl-3-methyl-2-{[4-(trifluoromethoxy)-phenyl]imino}-2,3-dihydro-1H-benzimidazol-1-yl)methyl]benzoate

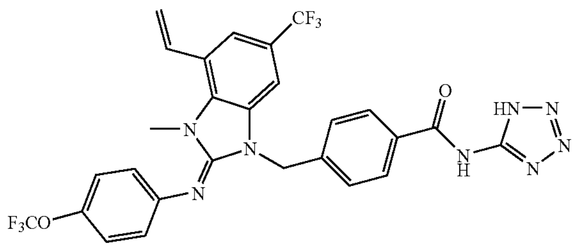
[0396] To a mixture of the title compound in Example 7, Step C (38 mg, 0.084 mmol) and sodium hydride (6.0 mg, 60% suspension in mineral oil, 0.15 mmol) was added DMF (1 mL). After ten min, methyl-4-(bromomethyl)benzoate (38 mg, 0.168 mmol) was added, and the mixture was stirred at room temperature. After 12 h, the mixture was diluted with CH_2Cl_2 and poured in saturated aq. $NaHCO_3$/brine (1:1). The phases were separated, and the organic phase was dried over Na_2SO_4 and concentrated. The crude reaction mixture, a ca. 5:1 mixture regioisomers, was taken forward directly: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J=8.0 Hz, 2H), 7.43 (s, 1H), 7.11 (d, J=8.5 Hz, 2H), 6.98 (d, J=8.5 Hz, 2H), 6.85 (s, 1H), 6.78 (d, J=8.0 Hz, 2H), 4.98 (s, 2H), 3.91 (s, 3H), 3.63 (s, 3H). LC-MS (ESI, Method B) 1.97 min, m/z 604.0 (M+1).

Step. E. 4-[(4-Bromo-3-methyl-2-{[4-(trifluoromethoxy)phenyl]-imino}-6-(trifluoromethyl)-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzamide

[0397] To a dioxane (1 mL) solution of the title compounds in Example 7, Step D was added LiOH (10 mg, 0.42 mmol) in 0.5 mL H_2O, and the reaction mixture was stirred at 40° C. After 1 h, reaction mixture was diluted with EtOAc and washed with pH 7 phosphate buffer. The aqueous phase was extracted twice with EtOAc, and the combined organic phases were dried over Na_2SO_4 and concentrated. To the crude mixture of carboxylic acids were added EDC (161 mg, 0.84 mmol), HOBt (128 mg, 0.84 mmol), DMF (1.5 mL), DIEA (219 μL, 1.26 mmol) and 1H-tetraazol-5-amine monohydrate monohydrate (86 mg, 0.84 mmol). The reaction mixture was stirred at 40° C. for 12 h, then concentrated in vacuo. Purification by reverse-phase chromatography (20-80% CH_3CN/H_2O, each with 0.1% TFA) and lyophilization provided the title compound as a white solid. ^{1}H NMR (500 MHz, d_6-DMSO) δ 12.40 (s, 1H), 7.99 (d, J=8.5 Hz, 2H), 7.57 (s, 1H), 7.51 (s, 1H), 7.25 (d, J=8.5 Hz, 2H), 7.12 (d, J=8.0 Hz, 2H), 6.90 (d, J=8.0 Hz 2H), 6.52 (br s, 1H), 5.22 (s, 2H), 3.57 (s, 3H); LC-MS (ESI, Method B) 1.75 min, m/z 655.0 (M+1).

EXAMPLE 8

[0398]



Step A. 1-methyl-N-[4-(trifluoromethoxy)phenyl]-5-(trifluoromethyl)-5-(trifluoromethyl)-7-vinyl-1H-benzimidazol-2-amine

[0399] A nitrogen-purged flask was charged with $AsPh_3$ (44 mg, 0.12 mmol) and $Pd_2(dba)_3$ (34 mg, 0.037 mmol). In a separate flask, the title compound from Example 7, Step C (165 mg, 0.363 mmol) and vinyl tributylstannane (200 μL, 0.68 mmol) were dissolved in DMF. This solution was degassed by sparging with nitrogen, then transferred to the flask containing $AsPh_3$ and $Pd_2(dba)_3$, and the reaction mixture was stirred for 15 h at 60° C. The mixture was then cooled to room temperature, filtered through Celite, washed with brine, and concentrated. Purification by flash chromatography (10% EtOAc in hexanes then 25% EtOAc in hexanes) provided the title compound as a white solid: LC-MS (ESI, Method B) 1.80 min, m/z 402.3 (M+1).

Step B. Methyl 4-[(3-methyl-2-{[4-(trifluoromethoxy)-phenyl]imino}-6-(trifluoromethyl)4-vinyl-2,3-dihydro-1H-benzimidazol-1-yl)methyl]benzoate

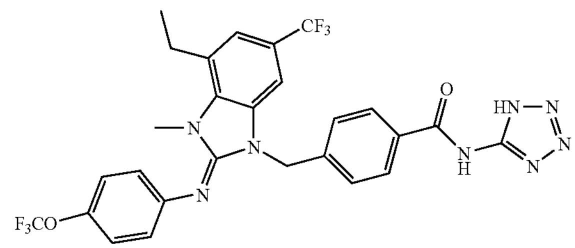
[0400] To a mixture of the title compound of Example 8, Step A (59 mg, 0.147 mmol) and sodium hydride (60% suspension in mineral oil, 8.9 mg, 0.221 mmol) was added DMF (1.5 mL). After ten min, methyl-4-(bromomethyl)benzoate (50.5 mg, 0.221 mmol) was added and the mixture was stirred at room temperature. After 1.5 h, the mixture was diluted with CH_2Cl_2 and poured in saturated aq. $NaHCO_3$/brine. The phases were separated, and the organic phase was dried over Na_2SO_4 and concentrated. The crude reaction mixture, a ca. 5:1 mixture of regioisomers, was taken forward directly: LC-MS (ESI, Method B) 1.95 min, m/z 550.3 (M+1).

Step C. 4-[(3-Methyl-2-{[4-(trifluoromethoxy)phenyl] imino}-6-(trifluoromethyl)4-vinyl-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzamide

[0401] To a solution of the title compounds from Example 8, Step B in dioxane (1 mL) was added LiOH (21 mg, 0.88 mmol) in 0.5 mL H_2O, and the reaction mixture was stirred at 40° C. After 1 h, the reaction mixture was diluted with EtOAc and washed with pH 7 phosphate buffer. The aqueous phase was extracted twice with EtOAc, and the combined organic phases were dried over Na_2SO_4 and concentrated. To the crude mixture of carboxylic acids were added EDC (253 mg, 1.32 mmol), HOBt (202 mg, 1.32 mmol), DMF (1 mL), DIEA (520 μL, 2.94 mmol) and 1H-tetraazol-5-amine monohydrate (151 mg, 1.47 mmol). The reaction mixture was stirred at 40° C. for 12 h, then concentrated under high vacuum. Purification by reverse-phase chromatography (20-80% CH_3CN/H_2O, both containing 0.1% TFA) followed by lyophilization provided the product as a white solid: ^1H NMR (d_6-DMSO, 500 MHz) δ 12.40 (s, 1H), 8.00 (d, J=8.0 Hz, 2H), 7.65-7.00 (m, 7H), 7.33 (d, J=8.0 Hz, 2H), 5.90-5.22 (m, 6H), N-Me obscured by H_2O peak; LC-MS (ESI, Method B) 1.79 min, m/z 603.3 (M+1).

EXAMPLE 9

[0402]



Step A. 7-Ethyl-1-methyl-5-N-[4-(trifluoromethoxy)phenyl]-5-(trifluoromethyl)-1H-benzimidazol-2-amine

[0403] A solution of the title compound of Example 8, Step A (50 mg, 0.12 mmol) in MeOH (5 mL) was degassed by sparging with nitrogen, then was charged with 10% Pd/C (60 mg). The suspension was placed under a hydrogen atmosphere (balloon) and stirred rapidly for 24 h. After filtration through Celite and concentration in vacuo, the crude product was taken forward directly: LC-MS (ESI, Method B) 1.77 min, m/z 404.0 (M+1).

Step B. Methyl 4-[(4-ethyl-3-methyl-2-{[4-(trifluoromethoxy)-phenyl]imino}-6-(trifluoromethyl)-2,3dihydro-1H-benzimidazol-1-yl)methyl]benzoate

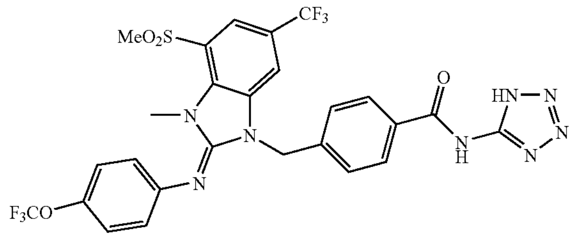
[0404] A flask containing the title compound from Example 9, Step A (36 mg, 0.089 mmol) was charged with sodium hydride (60% suspension in mineral oil, 5.4 mg, 0.134 mmol), and the mixture was dissolved in DMF (1.5 mL). After ten min, methyl-4-(bromomethyl)benzoate (31.5 mg, 0.134 mmol) was added and the mixture was stirred at room temperature. After 1.5 h, the mixture was diluted with CH_2Cl_2 and poured into saturated aq. $NaHCO_3$/brine. The phases were separated, and the organic phase was dried over Na_2SO_4 and concentrated. The crude reaction mixture, containing both N-benzylated regioisomers, was taken forward directly: LC-MS (ESI, Method B) 2.01 min, m/z 552.3 (M+1).

Step C. 4-[(4-Ethyl-3-methyl-2-{[4-(trifluoromethoxyphenyl]-imino}-6-(trifluoromethyl)-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzamide

[0405] To a solution of the crude product from Example 9, Step B in dioxane (1 mL) was added LiOH (12.8 mg, 0.53 mmol) in 0.5 mL H_2O, and the reaction mixture was stirred at 40° C. After 1 reaction mixture was diluted with EtOAc and washed with pH 7 phosphate buffer. The aqueous phase was extracted twice with EtOAc, and the combined organic phases were dried over Na_2SO_4 and concentrated. To the crude mixture of carboxylic acids were added EDC (154 mg, 0.80 mmol), HOBt (122 mg, 0.80 mmol), DMF (1.5 mL), DIEA (236 μL, 1.34 mmol) and 1H-tetraazol-5-amine monohydrate (92 mg, 0.89 mmol). The reaction mixture was stirred at 40° C. for 6 h, then concentrated under high vacuum. Purification by reverse-phase chromatography (20-65% CH_3CN/H_2O, both containing 0.1% TFA), followed by lyophilization, provided the product as a white solid: ^1H NMR (500 MHz, d_6-DMSO) δ 12.43 (s, 1H), 8.03 (d, J=8.0 Hz, 2H), 7.50-7.20 (m, 7H), 7.34 (d, J=8.0 Hz, 2 H), 5.51 (br s, 2H), 1.33 (t, J=7.0 Hz, 3H), C4-CH_2 and N-Me obscured by H_2O; LC-MS (ESI, Method A) 3.00 min, m/z 605.3 (M+1).

EXAMPLE 10

[0406]



Step A. 1-Methyl-7-(ethylsulfonyl)-N-[4-(trifluoromethoxy)phenyl]-5-(trifluoromethyl)-1H-benzimidazol-2-amine

[0407] To a suspension of the title compound from Example 7, Step C (45 mg, 0.10 mmol) and CuI (47 mg, 0.25 mmol) in DMSO (1 mL) was added sodium methanesulfinate (24 mg, 0.20 mmol), and the reaction mixture was stirred at 110° C. for 15 h. The mixture was allowed to cool to room temperature, then filtered through a cotton plug, and diluted with EtOAc. The filtrate was washed with water and brine, then concentrated in vacuo. Purification by flash chromatography (20% EtOAc in hexanes then 100% EtOAc) provided the title compound as a white solid: ^1H NMR (500 MHz, CD_3OD) δ 7.99 (s, 1H), 7.95 (s, 1H), 7.79 (d, J=8.5 Hz, 2H), 7.32 (d, J=8.5 Hz, 2H), 4.20 (s, 3H), 3.43 (s, 3H). LC-MS (ESI, Method B) 2.42 min, m/z 454.2 (M+1).

Step B. Methyl 4-[(3-methyl-4-methylsufonyl-2-{[4-(trifluoromethoxy)-phenyl]imino}-6-(trifluoromethyl)-2,3-dihydro-1H-benzimidazol-1-yl)methyl]benzoate

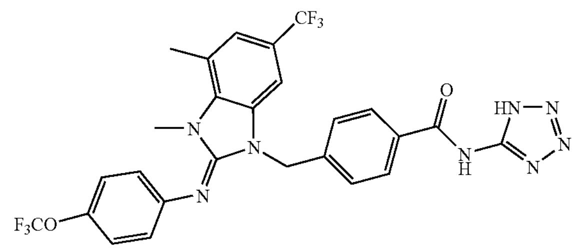
[0408] A flask containing the title compound from Example 10, Step A (30 mg, 0.066 mmol) was charged with sodium hydride (60% suspension in mineral oil, 4.0 mg, 0.10 mmol), and the mixture was dissolved in DMF (1.5 mL). After ten minutes, methyl4-(bromomethyl)benzoate (18 mg, 0.077 mmol) was added and the mixture was stirred at room temperature. After 15 h, the mixture was diluted with CH_2Cl_2 and poured in saturated aq. $NaHCO_3$/brine. The phases were separated, and the organic phase was dried over Na_2SO_4 and concentrated. The crude reaction mixture, containing both N-benzyl regioisomers, was taken forward directly: LC-MS (ESI, Method B) 2.25 min, m/z 602.3 (M+1).

Step C. 4-[(3-methyl4-methylsufonyl-2-{[4-(trifluoromethoxy)-phenyl]imino}-6-(trifluoromethyl)-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzamide

[0409] To a solution of the crude product from Example 10, Step B in dioxane (1 mL) was added LiOH (9.5 mg, 0.04 mmol) in 0.5 mL H_2O, and the reaction mixture was stirred at 40° C. After 1 h, the reaction mixture was diluted with EtOAc and washed with pH 7 phosphate buffer. The aqueous phase was extracted twice with EtOAc, and the combined organic phases were dried over Na_2SO_4 and concentrated. To the crude mixture of carboxylic acids were added EDC (113 mg, 0.59 mmol), HOBt (91 mg, 0.59 mmol), DMF (1 mL), DIEA (230 μL, 1.32 mmol) and 1H-tetraazol-5-amine monohydrate (68 mg, 0.66 mmol). The reaction mixture was stirred at 40° C. for 12 h, then concentrated under high vacuum. Purification by reverse-phase chromatography (20-80% CH_3CN/H_2O, both containing 0.1% TFA), followed by lyophilization, provided the product as a white solid: ^1H NMR (500 MHz, d_6-DMSO) δ 12.40 (s, 1H), 8.00 (d, J=8.5 Hz, 2H), 7.84 (s, 1H), 7.79 (s, 1H), 7.22 (d, J=8.5 Hz, 2H), 7.20 (br s, 1H), 7.12 (d, J=8.0 Hz, 2H), 6.87 (d, J=8.0 Hz, 2H), 5.24 (s, 2H), 3.66 (s, 3H), 3.56 (s, 3H); LCMS (ESI,) 1.97 min, m/z 655.2 (M+1).

EXAMPLE 11

[0410]



Step A. 1,7-Dimethyl-N-[4-(trifluoromethoxy)phenyl]-5-(trifluoromethyl)-1H-benzimidazol-2-amine

[0411] A nitrogen-purged flask was charged with $AsPh_3$ (32 mg, 0.0.88 mmol) and $Pd_2(dba)_3$ (20 mg, 0.022 mmol). In a separate flask, the title compound from Example 7, Step C (100 mg, 0.22 mmol) and tetramethyltin (40 μL, 0.29 mmol) were dissolved in DMF (1.5 ml). This solution was then transferred to the flask containing $AsPh_3$ and $Pd_2(dba)_3$, and the reaction mixture was stirred for 15 h at 75° C. The mixture was then cooled to room temperature, filtered through Celite, washed with brine, and concentrated. Purification by flash chromatography (10% EtOAc/hexanes then 25% EtOAc/hexanes) provided the title compound as a colorless oil: LC-MS (ESI, Method B) 2.06 min, m/z 390.2 (M+1).

Step B. Methyl 4-[(3,4-dimethyl-2-{[4-(trifluoromethoxy)-phenyl]imino}-6-(trifluoromethyl)-2,3-dihydro-1H-benzimidazol-1-yl)methyl]benzoate

[0412] A flask containing the title compound from Example 11, Step A (20 mg, 0.051 mmol) was charged with sodium hydride (60% suspension in mineral oil, 3.0 mg, 0.077 mmol), and the mixture was dissolved in DMF (1 mL). After ten minutes, methyl-4-(bromomethyl)benzoate (18 mg, 0.077 mmol) was added and the mixture was stirred at room temperature. After 15 h, the mixture was diluted with CH_2Cl_2 and poured in saturated aq. $NaHCO_3$/brine.

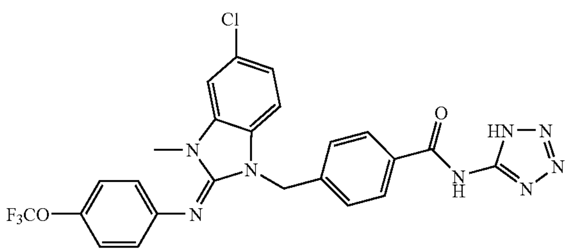
The phases were separated, and the organic phase was dried over Na_2SO_4 and concentrated. The crude reaction mixture, containing both N-benzyl regioisomers, was taken forward directly: LC-MS (ESI, Method B) 2.24 min, m/z 538.1 (M+1); 2.60 min, m/z 538.1 (M+1).

Step C. 4-[(3,4-dimethyl-2-{[4-(trifluoromethoxy)-phenyl]imino}-6-(trifluoromethyl)-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzamide

[0413] To a solution of the crude product from Example 11, Step B in dioxane (1 mL) was added LiOH (10 mg, 0.04 mmol) in 0.5 mL H_2O, and the reaction mixture was stirred at 40° C. After 1 h, the reaction mixture was diluted with EtOAc and washed with pH 7 phosphate buffer. The aqueous phase was extracted twice with EtOAc, and the combined organic phases were dried over Na_2SO_4 and concentrated. To the crude mixture of carboxylic acids were added EDC (113 mg, 0.59 mmol), HOBt (91 mg, 0.59 mmol), DMF (1 mL), DIEA (230 μL, 1.29 mmol) and 1H-tetraazol-5-amine monohydrate (68 mg, 0.66 mmol). The reaction mixture was stirred at 40° C. for 12 h, then concentrated under high vacuum. Purification by reverse-phase chromatography (20-75% CH_3CN/H_2O, both containing 0.1% TFA), followed by lyophilization, provided the product as a white solid: ^1H NMR (500 MHz, d_6-DMSO) δ 12.40 (s, 1H), 8.01 (d, J=8.0 Hz, 2H), 7.60-6.50 (m, 7H), 7.33 (d, J=8.0 Hz, 2H), 5.47 (s, 2H), 3.64 (s, 3H), 3.62 (s, 3H); LC-MS (ESI, Method B) 2.00 min, m/z 591.3 (M+1).

EXAMPLE 12

[0414]



Step A. Methyl 4-{[(4-chloro-2-nitrophenyl)amino]methyl}benzoate

[0415] To 4-chloro-2-nitroaniline (10 mmol, 1.73 g) in DMF (10 mL) was added NaH (11 mmol, 440 mg of 60% suspension in mineral oil). After 30 min the reaction vessel was placed in a water bath and methyl-4-(bromomethyl)benzoate (11 mmol, 2.52 g) was added (exothermic). The reaction mixture was allowed to stand at ambient temperature for 16 h, then poured into saturated $NaHCO_3$, affording an orange precipitate which was filtered, washed with water and dried in vacuo. Purification by flash chromatography on silica eluting with 15% EtOAc in hexanes provided the product as an orange solid. LC-MS (ESI, Method C) 3.79 min, m/z 321.1 (M+1).

Step B. Methyl 4-{[(2-amino-4-chlorophenyl)amino]methyl}benzoate

[0416] The title compound of Example 12, Step A (3.6 mmol, 1.2 g) and $SnCl_2.2H_2O$ (18 mmol, 4 g) were heated in DMP (10 mL) at 40° C. for 3 hr. The reaction mixture was poured into EtOAc and concentrated $NaHCO_3$ and stirred. The resulting mixture was filtered over celite, and the filter cake was washed with EtOAc. The organic phase was collected, dried with Na_2SO_4 and reduced in vacuo. Flash chromatography on silica eluting with 20% and 30% EtOAc in hexanes afforded the product as a pale white solid. ^1H NMR (500 MHz, d_6-DMSO) δ 7.94 (d, J=8.2 Hz, 2H), 7.49 (d, J=8.2 Hz, 2H), 6.70 (s, 1H), 6.32 (s, 1H), 5.68 (t, J=5.8 Hz, 1H), 5.07 (s, 2H), 4.41 (d, J=5.7 Hz, 2H), 3.85 (s, 3H). LC-MS (ESI, Method C) 3.33 min, 291.2 (M+1).

Step C. Methyl 4-[(5-chloro-2-{[4-(trifluoromethoxy)-phenyl]amino}-1H-benzimid-azol-1-yl)methyl]benzoate

[0417] The title compound of Example 12, Step B (0.5 mmol, 145 mg) and 4-trifluoromethoxyphenyl isothiocyanate (0.5 mmol, 81 μL) were heated in DCM (1 mL) for 1 h, then allowed to stand at ambient temperature for 16 h. MeI (1.0 mmol, 62 μL), DIEA (1.0 mmol, 174 μL) and DMF (0.5 mL) were added and the solution was heated at 40° C. for 2 h. The reaction mixture was partitioned between EtOAc/brine and the organic phase was dried with Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica eluting with 18% EtOAc in hexanes afforded the product as a beige solid. LC-MS (ESI, Method C): 3.85 min, m/z 476.1 (M+1).

Step D. Methyl 4-[(5-chloro-3-methyl-2-{[4-(trifluoromethoxy)-phenyl]imino}-2,3-dihydro-1H-benzimidazol-1-yl)methl]benzoate

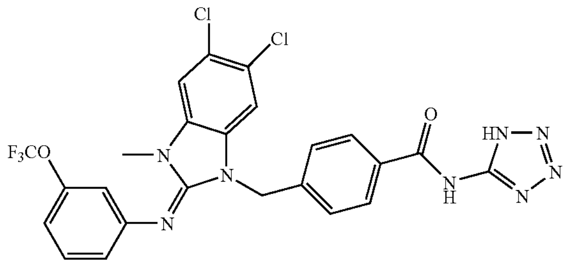
[0418] The title compound in Example 12, Step C (0.08 mmol, 36 mg) and NaH (0.1 mmol, 4 mg of a 60% suspension in mineral oil) were taken up in DMF (0.5 mL). After 10 min. MeI (0.15 mmol, 9 μL) was added and the reaction was allowed to stand at ambient temperature. After 1 h the reaction was partitioned into $NaHCO_3/CH_2Cl_2$. The organic phase was dried over Na_2SO_4 and reduced in vacuo to afford a mixture of N-methyl regioisomers, which was taken on directly. LC-MS (ESI, Method C) 2.95 min, m/z 490.0 (M+1).

Step E. 4-[(5-Chloro-3-methyl-2-{[4-(trifluoromethoxy)phenyl]-imino}-2,3-dihydro-1H-benzimidazol-1-l)methyl]-N-1H-tetrazol-5-ylbenzamide

[0419] The residue from Example 12, Step D was taken up in dioxane (1 mL) and a solution of LiOH (1 mmol, 24 mg) in H_2O (0.5 mL) was added. The reaction was stirred at 40° C. for 1 h, then partitioned between EtOAc and brine buffered to pH 7. The organic phase was dried with Na_2SO_4 and reduced in vacuo. To the residue was added a solution of 1H-tetraazol-5-amine monohydrate (0.2 mmol, 21 mg), EDC (0.2 mmol, 38 mg), HOBt (0.2 mmol, 31 mg) and DIEA (0.3 mmol, 52 μL) in DMF (1 mL). The reaction mixture was heated for 2 h at 40° C. Reverse-phase chromatography (20-60% $MeCN/H_2O$, both containing 0.1% TFA) and lyophilization afforded the product as a white solid. ^1H NMR (500 MHz, d_6-DMSO) δ 12.42 (s, 1H), 8.04 (d, J=8.4 Hz, 2H), 7.87 (br m, 1H), 7.45 (br m, 1H), 7.39 (br m, 1H), 7.36 (d, J=8.2 Hz, 2H), 7.31 (br d, J=8.2 Hz, 2H), 7.24 (br m, 2H), 5.45 (s, 2H), N-Me obscured by H_2O peak. LC-MS (ESI, Method C) 2.50 min, m/z 543.1 (M+1).

EXAMPLE 13

[0420]



Step A. Methyl 4-{[(2-amino-4,5-dichlorophenyl)amino]methyl}benzoate

[0421] 4,5-Dichloro-2-nitroaniline (10 mmol, 2.07 g), 4-bromomethylbenzoate (10 mmol, 2.29 g) and K_2CO_3 (12 mmol, 1.66 g) were stirred in DMF (10 mL) at ambient temperature for 16 h. The reaction mixture was partitioned between CH_2Cl_2 and brine, and the organic phase was dried with Na_2SO_4 and concentrated in vacuo. The monobenzylated product was obtained by flash chromatography on silica eluting with 15% EtOAc in hexanes as a bright orange solid. A portion of the nitro compound (7.4 mmol, 2.6 g) and $SnCl_2$.2 H_2O (22 mmol, 5.0 g) were heated in 40 mL of DMF at 40° C. for 16 h. The reaction mixture was poured into EtOAc and saturated $NaHCO_3$ and stirred to afford a precipitate, which was removed by filtration through celite. The organic phase was dried with Na_2SO_4 and concentrated in vacuo to a brown oil. Flash chromatography on silica eluting with a step gradient of 20%, 30% and 35% EtOAc in hexanes provided the product as a pale yellow solid. LC-MS (ESI, Method C) 3.54 min, m/z 325.2 (M+1).

Step B. Methyl 4-[(5,6-dichloro-2-{[3-(trifluoromethoxy)phenyl]amino}-1H-benzimid-azol-1-yl)methyl]benzoate

[0422] To a solution of 3-trifluoromethyoxyphenylaniline (0.2 mmol, 35 mg, 27 µL) and DIEA (0.5 mmol, 87 µL) in 0.5 mL of CH_2Cl_2 was added thiophosgene (0.2 mmol, 15 µL) via syringe. The solution was allowed to stand at ambient temperature for 1 h, and the title compound in Example 13, Step A (0.2 mmol, 65 mg) was added. The reaction mixture was heated at 40° C. for 1 h, then $Hg(O_2CCF_3)_2$ was added. The reaction was heated at 40° C. for 2 h, and allowed to stand at ambient temperature for 16 h. The slurry was poured into EtOAc and saturated $NaHCO_3$ containing Na_2S, then filtered through celite. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica eluting with 20% and 35% EtOAc in hexanes afforded the product as a beige solid. LC-MS (ESI, Method B) 2.14 min, m/z 524.1 (M+1).

Step C. Methyl 4-[(5,6-dichloro-3-methyl-2-{[3-(trifluoromethoxy)-phenyl]imino}-2,3-dihydro-1H-benzimidazol-1-yl)methyl]benzoate

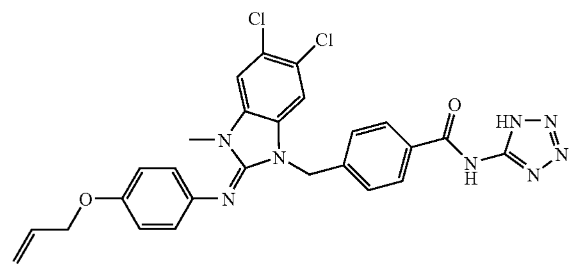
[0423] The title compound in Example 13, Step B (0.1 mmol, 51 mg) and NaH (0.2 mmol, 8 mg of a 60% suspension in mineral oil) were taken up in 0.7 mL of DMF. After 10 min MeI (0.2 mmol, 13 µL) was added to the reaction. After 15 h the reaction was not complete, so an additional 0.2 mmol of NaH and MeI were added to the reaction. After 2 h the reaction was partitioned between $NaHCO_3$/DCM. The organic phase was dried over Na_2SO_4 and reduced in vacuo. The product was isolated by preparative TLC on silica eluting with 20% EtOAc/hexanes (LC-MS), and taken on directly. LC-MS (ESI, Method B) 2.38 min, m/z 510.2 (M+1).

Step D. 4-[(5,6-Dichloro-3-methyl-2-{[3-(trifluoromethoxy)phenyl]-imino}-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzamide

[0424] To a solution of the title compound of Example 13, Step C in dioxane (4 mL), was added a solution of LiOH (2 mmol, 48 mg) in H_2O (2 mL). The reaction was stirred at ambient temperature for 16 h, then was partitioned into EtOAc/brine buffered to pH 7. The organic phase was dried with Na_2SO_4 and concentrated in vacuo. To the residue was added a solution of ^{1}H-tetraazol-5-amine monohydrate (0.2 mmol, 21 mg), EDC (0.2 mmol, 38 mg), HOBt (0.2 mmol, 31 mg) and DIEA (0.3 mmol, 52 µL) in DMF (1 mL). The resulting reaction mixture was heated for 2 h at 40° C., and the product was isolated by reverse-phase chromatography (20-60% $MeCN/H_2O$, both containing 0.1% TFA). Lyophilization afforded the product as a white solid. ^{1}H NMR (500 MHz, d_6-DMSO) δ 12.42 (s, 1H), 8.05 (d, J=8.2 Hz, 2H), 7.85 (br s, 1H), 7.70 (br s, 1H), 7.35-7.42 (overlapping m, 3H), 6.97-7.09 (overlapping m, 3H), 5.36 (s, 2H), 3.33 (s, 3H). LC-MS (ESI, Method B) 1.93 min, m/z 577.0 (M+1).

EXAMPLE 14

[0425]



Step A. 4-(Allyloxy)aniline

[0426] To a solution of 4-nitrophenol (20 mmol, 2.78 g) in DMT (12 mL) was added K_2CO_3 (24 mmol, 3.31 g) and alkyl bromide (20 mmol, 1.73 mL). The slurry was stirred for 16 h at ambient temperature, then partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was dried with Na_2SO_4 and concentrated in vacuo to afford a brown oil. The oil was taken up in 10% H_2O/DMF (33 mL). $SnCl_2.2H_2O$ (77 mmol, 17.3 g) was added and the reaction was stirred at 40° C. for 16 h. The mixture was poured into saturated $NaHCO_3$ and CH_2Cl_2 and stirred briefly, then filtered through celite. The organic phase was collected and dried with $MgSO_4$ and concentrated in vacuo. Flash chromatography on silica eluting with 20% EtOAc in hexanes afforded the product as a brown oil. LC-MS (ESI, Method B): 1.09 min, m/z 150.1 (M+1).

Step B. N-[4-(Allyloxy)phenyl]-5,6-dichloro-1H-benzimidazol-2-amine

[0427] To a stirring solution of the title compound of Example 14, Step A (2.5 mmol, 373 mmol) and DIEA (2.75 mmol, 478 μL) in CH_2Cl_2 (4 mL) at 0° C. was added thiophosgene (2.5 mmol, 191 μL). The solution was allowed to reach ambient temperature for 1 h, and 4,5-dichloro-1,2-phenylenediamine (2.5 mmol, 443 mg) was added to the reaction. The reaction mixture was heated to 40° C. for 16 h. MeI (5 mmol, 312 μL) was added, and the reaction was heated at 40° C. for 16 h. Aqueous workup with CH_2Cl_2 and brine, followed by flash chromatography on silica eluting with 3% MeOH in CH_2Cl_2 afforded the product as a brown solid. LC-MS (ESI, Method B): 1.79 min, m/z 334.1 (M+1).

Step C Methyl 4-[(2-{[4-(alkyloxy)phenyl]amino}-5,6-dichloro-1H-benzimidazol-1-yl)methyl]benzoate

[0428] To the title compound of Example 14, Step B (2.2 mmol, 720 mg) in DMF (5 mL) was added NaH (2.6 mmol, 105 mg of 60% suspension in mineral oil). After 5 min methyl-4-(bromomethyl)benzoate (2.2 mmol, 502 mg) was added and the reaction mixture was left at ambient temperature for 16 h. Aqueous workup in CH_2Cl_2/brine, followed by flash chromatography on silica eluting with 3% MeOH in CH_2Cl_2 afforded the product as a brown oil. LC-MS (ESI, Method B): 2.07 mnin, m/z 482.2 (M+1).

Step D. Methyl 4-[(2-{[4-(alkyloxy)-phenyl]imino}-5,6-dichloro-3-methyl-2,3-dihydro-1H-benzimidazol-1-yl)methyl]benzoate

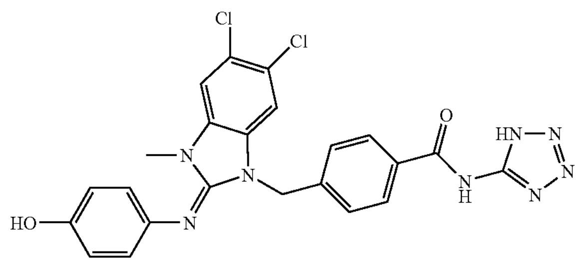
[0429] To a solution of the title compound of Example 14, Step C (0.1 mmol, 46 mg) in DMF (1 mL) was added NaH (0.12 mmol, 5 mg of 60% suspension in mineral oil). After 5 min MeI (0.2 mmol, 12 μL) was added. After 1.5 h the reaction mixture was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was dried with $MgSO_4$ and concentrated in vacuo to afford the product and the N-methyl regioisomer. LC-MS (ESI, Method B): 2.06 miln, m/z 496.2 (M+1).

Step E. 4-[(2-{[4-(Allyloxy)-phenyl]imino}-5,6-dichloro-3-methyl-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzamide

[0430] To the product of Example 14, Step D (0.6 mmol, 30 mg) dissolved in 0.8 mL of dioxane was added a solution of LiOH (0.4 mmol, 10 mg) in 0.4 mL of H_2O. The reaction was stirred at 40° C. fo 1 h, then partitioned between EtOAc/pH 7 phosphate buffer. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure to afford an amber foam. The foam was taken up in a solution of 1H-tetraazol-5-amine monohydrate (0.18 mmol, 19 mg), HOBt (0.12 mmol, 18 mg), EDC (0.12 mmol, 23 mg) and DIEA (0.18 mmol, 31 μL) in DMF (1 mL). The reaction mixture was heated to 40° C. for 1 h, then concentrated under reduced pressure. The residue was taken up in 2:1 dioxane/H_2O, acidified with TFA, and purified by reverse-phase chromatography (20-60% MeCN/H_2O, both containing 0.1% TFA). Lyophilization afforded the title compound as a white solid. ^1H NMR (d_6-DMSO+NEt_3, 500 MHz) δ 7.90 (br d, J=7.1 Hz, 2H), 7.35 (s, 1H), 7.28-7.26 (overlapping s, d, 3H), 6.79 (m, 2H), 6.76 (m, 2H), 6.03 (m, 1H), 5.39 (dd, J=15.6 Hz, 1.8 Hz, 1H), 5.25 (d, J=10.3 Hz, 1H), 5.08 (s, 2H), 4.50 (d, J=5.2 Hz, 2H), 3.12 (s, 3H). LC-MS (ESI, Method A): 2.99 min, m/z=549.2 (M+1).

EXAMPLE 15

[0431]

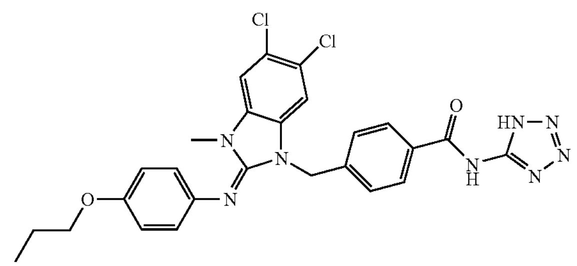


4-[(5,6-Dichloro-2-{[4-(hydroxy)phenyl]-imino}-3-methyl-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzamide

[0432] Pd_2.dba$_3$ (0.025 mmol, 23 mg) and 1,4-bis(diphenylphosphinyl)butane (0.05 mmol, 21 mg) were combined in 0.5 mL of THF under N_2. After 15 min the Pd solution was transferred via syringe to a separate flask containing the title compound of Example 14, Step E (0.015 mmol, 8 mg) and 1,3-dimethylbarbituric acid (0.02 mmol, 3 mg) in CH_2Cl_2 (0.7 mL). The reaction was allowed to stand at ambient temperature for 1 h. Reverse-phase chromatography (10-80% MeCN/H_2O, both containing 0.1% TFA), and lyophilization provided the product as a white solid. ^1H NMR (d_6-DMSO+NEt_3, 500 MHz) δ 7.90 (broad d, 2H), 7.32 (s, 1H), 7.29 (broad d, 2H), 7.25 (s, 1H), 6.65 (m, 2H), 6.61 (m, 2H), 5.10 (s, 2H), 3.10 (s, 3H). LC-MS (ESI, Method A): 2.71 min, m/z 509.1 (M+1).

EXAMPLE 16

[0433]



Step A. Methyl 4-[(5,6-dichloro-2-{[4-(hydroxy)-phenyl]imino}-3-methyl-2,3-dihydro-1H-benzimidazol-1-yl)methyl]benzoate

[0434] Pd_2dba_3 (0.025 mmol, 23 mg) and 1,4-bis(diphenylphosphinyl)butane (0.05 mmol, 21 mg) were combined in 0.5 mL of THF under N_2. After 15 min the Pd solution was transferred via syringe to a separate flask containing the title compound of Example 14, Step D (0.1 mmol, 55 mg) and 1,3-dimethylbarbituric acid (0.12 mmol, 19 mg) in DCM (1 mL). The reaction mixture was allowed to stand at ambient temperature for 1 h. The product was isolated by chromatography on silica eluting with 3% MeOH in CH_2Cl_2. LC-MS (ESI, Method B): 1.86 mim, m/z 456.1 (M+1).

Step B. Methyl 4-[(5,6-dichloro-3-methyl-2-{[4-(propyloxy)-phenyl]imino}-2,3-dihydro-1H-benzimidazol-1-yl)methyl]benzoate

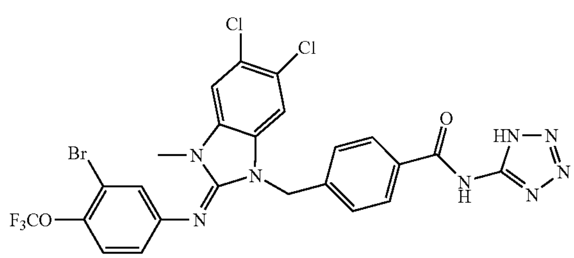
[0435] To the title compound of Example 16, Step A (0.04 mmol, 20 mg) in CH_2Cl_2 (0.7 mL) was added 1-propanol (0.1 mmol, 7 μL), DIAD (0.08 mmol, 16 μL) and Ph_3P (0.08 mmol, 11 mg). After 1 h the reaction was not complete, so additional 1-propanol (0.1 mmol), DIAD (0.8 mmol) and Ph_3P (0.08 mmol) were added. After 4 h the product was isolated by flash chromatography on silica eluting with 10% and 25% EtOAc in hexanes as a colorless oil. LC-MS (ESI, Method A): 3.40 min, m/z 498.2 (M+1).

Step C. 4-[(5,6-Dichloro-3-methyl-2-{[4-(propyloxy)phenyl]-imino}-2,3-dihydro-1H-benz-imidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzamide

[0436] To the title compound of Example 16, Step B (0.04 mmol, 19 mg) dissolved in 0.8 mL of dioxane was added a solution of LiOH (0.4 mmol, 10 mg) in 0.4 mL of H_2O. The reaction was stirred at 40° C. for 2 h. The product was partitioned between EtOAc/pH 7 phosphate buffer. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure to provide a white foam. To the foam was added a solution of 1H-tetraazol-5-amine monohydrate (0.12 mmol, 12 mg), HOBt (0.08 mmol, 12 mg), EDC (0.08 mmol, 15 mg) and DIEA (0.12 mmol, 21 μL) in DMF (1 mL). The reaction mixture was heated to 40° C. for 2 h, then concentrated under reduced pressure. Purification by reverse-phase chromatography (20-60% MeCN/H_2O, both containing 0.1% TFA), and lyophilization afforded the title compound as a white solid. ^{1}H NMR (d_6-DMSO+NEt_3, 500 MHz) δ 7.90 (broad d, J=6.8 Hz, 2H), δ 7.34 (s, 1H), δ 7.29-7.26 (overlapping s, d, 3H), δ 7.78-7.74 (overlapping m, 4H), δ 5.08 (s, 2H), δ 3.86 (t, J=6.4 Hz, 2H), δ 3.11 (s, 3H), δ 1.71 (m, J=7.3 Hz, 2H), δ 0.97 (t, obscured by NEt_3). LC-MS (ESI, Method A): 2.97 min, m/z 551.2 (M+1).

EXAMPLE 17

[0437]



Step A. Methyl 4-[(2-{[3-bromo-4-(trifluoromethoxy)-phenyl]amino}-5,6-dichloro-1H-benzimidazol-1-yl)methyl] benzoate

[0438] To a flask containing 3-bromo-4-trifluoromethoxyaniline (2 mmol, 512 mg) and DIEA (4.5 mmol, 780 μL) in CH_2Cl_2 (10 mL) in a cold water bath was added thiophosgene (2 mmol, 153 μL) (exothermic). After 30 min 4,5-dichloro-1,2-phenylenediamine (2.2 mmol, 389 mg) was added. After 1 h MeI (4 mmol, 2.28 mg) and DIEA (2.3 mmol, 400 μL) were added, and the resulting solution was allowed to stand at ambient temperature for 16 h. The reaction mixture was partitioned between sat. $NaHCO_3$ and CH_2Cl_2 and the organic phase was washed with brine, dried with Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica eluting with 30% and 40% EtOAc in hexanes provided the benzimidazole as a beige solid. To a portion of the solid (0.4 mmol, 176 mg) in DMF (2 mL) was added NaH (0.44 mmol, 18 mg of 60% suspension in mineral oil). After 10 min methyl-4-(bromomethyl)benzoate (0.4 mmol, 92 mg) was added and the reaction mixture was left at ambient temperature for 5 h. The reaction mixture was poured into saturated $NaHCO_3$, causing formation of a precipitate, which was filtered, washed with water and dried in vacuo. Flash chromatography on silica eluting with 25% and 35% EtOAc in hexanes afforded the product as a beige solid. ^{1}H NMR (500 MHz, d_6-DMSO) δ 9.65 (s, 1H), 8.41 (d, J=2.7 Hz, 1H), 7.89-7.96 (overlapping m, 3H), 7.74 (s, 1H), 7.58 (s, 1H), 7.53 (m, 1H), 7.26 (d, J=8.5 Hz, 2H), 5.67 (s, 2H), 3.82 (s, 3H). LC-MS (ESI, Method B): 2.68 min, m/z 590.0 (M+1).

Step B. Methyl 4-[(2-{[3-bromo4-(trifluoromethoxy)-phenyl]imino}-5,6-dichloro-3-methyl-1H-benzimidazol-1-yl-)methyl]benzoate

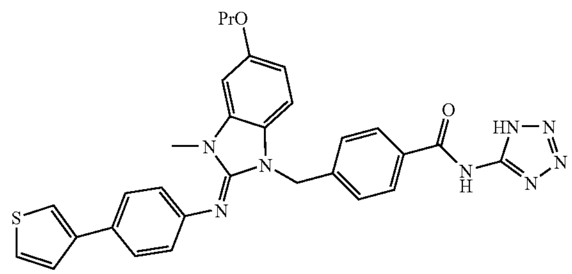
[0439] To a solution of the title compound of Example 17, Step A (0.15 mmol, 88 mg) in DMF (1 mL) was added NaH (0.2 mmol, 8 mg of 60% suspension in mineral oil). After 5 min MeI (0.2 mmol, 13 μL) was added. After 2 h the reaction mixture poured into saturated $NaHCO_3$, causing formation of a precipitate which was filtered, washed with water and dried in vacuo. Preparative TLC on silica with a mobile phase of 25% EtOAc in hexanes afforded the product as a white solid. LC-MS ESI, Method C) 4.18 min, m/z 604.0 (M+3).

Step C. 4-[(2-{[3-bromo-4-(trifluoromethoxy)-phenyl] imino}-5,6-dichloro-3-methyl-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzamide

[0440] To the title compound of Example 17, Step B (0.06 mmol, 35 mg) dissolved in dioxane (2 mL) was added a solution of LiOH (1.0 mmol, 24 mg) in H_2O (1 mL). The reaction was stirred at 40° C. for 2 h, and at ambient temperature for 16 h. The product was partitioned between EtOAc and brine buffered to pH 7. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure to afford a white solid. To the solid was added a solution of 1H-tetraazol-5-amine monohydrate (0.2 mmol, 21 mg), HOBt (0.2 mmol, 31 mg), EDC (0.2 mmol, 38 mg) and DIEA (0.3 mmol, 52 μL) in DMF (1 mL). The reaction mixture was heated to 40° C. for 2 h, then allowed to stand at ambient temperature for 16 h. The solution was concentrated under reduced pressure, and the residue was taken up in ca. 2:1 dioxane/H_2O, acidified with TFA, and purified by reverse-phase chromatography (20-60% MeCN in H_2O, both containing 0.1% TFA). Lyophilization afforded the title compound as a white solid. ^{1}H NMR (500 MHz, d_6-DMSO) δ 12.39 (s, 1H), 8.01 (d, J=8.4 Hz, 2H), 7.68 (s, 1H), 7.55 (s, 1H), 7.28-7.34 (overlapping m, 3H), 7.24 (s, 1H), 6.97 (m, 1H), 5.21 (s, 2H), 3.26 (s, 3H). LC-MS (ESI, Method C): 3.59 min, m/z 657.0 (M+3).

EXAMPLE 18

[0441]



Step A. 2-Fluoro-4-propoxynitrobenzene

[0442] To a solution of the 3-fluoro-4-nitrophenol (32 mmol, 5.0 g), 1-propanol (48 mmol, 3.9 mL), and triphenylphosphine (64 mmol, 16.8 g) in CH_2Cl_2 (160 mL) at 0° C. was added DIAD (64 mmol, 12 mg). The reaction mixture was concentrated in vacuo. The product was isolated by flash chromatography on silica eluting with 5% EtOAc in hexanes. H^1 NMR (500 MHz, $CDCl_3$): δ 8.13 (t, J=8.7 Hz, 1H), 6.81-6.75 (m, 2H), 4.05 (d, J=6.4 Hz, 2H), 1.90 (m, 2H), 1.10 (t, J=7.3 Hz, 3H).

Step B. N-Methyl-2-nitro-5-propoxyaniline

[0443] To a solution of the title compound in Example 18, Step A (32 mmol, 6.4 g) in methanol (20 mL) was added methylamine (2.0 M in methanol, 22 nL). After 16 h, the reaction mixture was concentrated in vacuo to afford a yellow solid. H^1 NMR (500 MHz, $CDCl_3$) δ 8.18 (d, J=9.6 Hz, 1H), 6.28 (dd, J=2.5, 9.4 Hz, 1H), 6.17 (d, J=2.5 Hz, 1H), 4.04 (t, J=6.4 Hz, 2H), 3.04 (d, J=5.1 Hz, 3H), 1.88 (m, 2H), 1.10 (t, J=7.5Hz, 3H). LC-MS (ESI, Method C) 3.43 min, m/z 211.2 (M+1).

Step C. N^1-Methyl-5-propoxybenzene-1,2-diamine

[0444] To a solution of the title compound in Example 18, Step B (0.492 mmol, 45 mg) in methanol (20 mL) was added palladium hydroxide on carbon (20% by weight, 60 mg). The reaction was stirred under a balloon of hydrogen. After 1.5 h, the reaction mixture concentrated in vacuo, redissolved in ethylacetate, washed with brine, dried with Na_2SO_4, and concentrated in vacuo. H^1 NMR (500 MHz, d_6-DMSO): δ 6.63 (d, J=8.2 Hz, 1H), 6.27 (d, J=2.5 Hz, 1H), 6.19 (d, J=7.1 Hz, 1H), 3.88 (t, J=6.6 Hz, 2H), 3.23 (bs, 1H), 2.84 (s, 3H), 1.80 (m, 2H), 1.04 (t, J=7.5 Hz, 3H). LC-MS (ESI, Method B) 1.37 min, m/z 181.1 (M+1).

Step D. N-[4-iodophenyl]-1-methyl-6-propoxy-1H-benzimidazol-2-amine

[0445] To a solution of the title compound in Example 18, Step C (2.7 mmol, 487 mg) in CH_2Cl_2 (5 mL) was added 4-iodophenyl isothiocyanate (2.25 mmol, 588 mg). After 1.5 h mercury trifluoroacetate (2.7 mmol, 1.2 g) was added. Dimethylformamide was added (5 mL). The reaction mixture was heated at 40° C. for 1 h. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with saturated $NaHCO_3$, dried with Na_2SO_4, and concentrated in vacuo to afford an oil. The product was isolated by flash chromatography on silica eluting with 15 to 85% EtOAc in hexanes. LC-MS (ESI, Method B): 1.99 min, m/z 408.0 (M+1).

Step E. Methyl 4-[(2-{[4-iodophenyl]imino}-3-methyl-5-propoxy-2,3-dihydro-1H-benzimidazol-1-yl)methyl]benzoate

[0446] To the title compound of Example 18, Step D (0.66 mmol, 271 mg) in DMF (6 mL) was added NaH (0.73 mmol, 29 mg of a 60% suspension in mineral oil). After 10 min methyl-4-(bromomethyl)benzoate (0.80 mmol, 183 mg) was added and the reaction mixture was stirred at ambient temperature for 10 min. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with saturated NH_4Cl dried with Na_2SO_4, and concentrated in vacuo to afford an oil. The product was isolated by flash chromatography on silica eluting with 15 to 60% EtOAc in hexanes. LC-MS (ESI, Method B): 1.95 min, m/z 558.0 (M+1).

Step F. Methyl 4-[(3-methyl-5-propoxy-2-{[4-(3-thienyl)phenyl]imino}-2,3dihydro-1H-benzinidazol-1-yl)methyl]benzoate

[0447] To the title compound of Example 18, Step E (100 mg, 0.18 mmol), 3-thienyl boronic acid (25 mg, 0.20 mmol), tri(o-tolyl)phosphine (11 mg, 0.04 mmol), and cesium carbonate (117 mg, 0.36 mmol) in DMF was degassed. Palladium acetate (2.4 mg, 0.01 mmol) was added, and the reaction was stirred overnight at 60° C. The reaction was diluted with ethyl acetate, washed with water and brine, and dried over Na_2SO_4. The product was isolated by flash chromatography on silica eluting with 15% EtOAc in hexanes. LC-MS (ESI, Method B): 1.99 min, m/z 512.0 (M+1)

Step G. 4-[(3-Methyl-5-propoxy-2-{[4-(3-thienyl)phenyl]imino}-2,3-dihydro-1H-benzimidazol-1-yl)methyl]benzoic acid

[0448] To the title compound of Example 18, Step F (0.16 mmol, 80 mg) in dioxane (6 mL) was added a solution of LiOH (2.1 mmol, 50 mg) in H_2O (4 mL). The reaction was stirred at 50° C. for 2.5 h. The product was partitioned between EtOAc and saturated NH_4Cl. The organic phase was washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure, affording the product as a yellow foamy solid which was taken on directly. LC-MS (ESI, Method B): 1.86 min, m/z 498.0 (M+1)

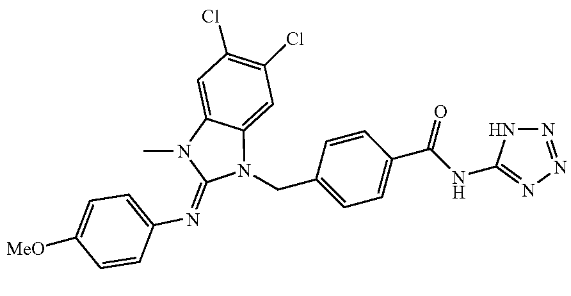
Step H. 4-[(3-Methyl-5-propoxy-2-{[4-(3-thienyl)phenyl]imino}-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzamide

[0449] To the title compound of Example 18, Step G (0.18 mmol, 88 mg) was added a solution of 1H-tetraazol-5-amine monohydrate (0.72 mmol, 74 mg), HOBt (0.72 mmol, 110 mg), EDC (0.72 mmol, 138 mg) and DIEA (1.08 mmol, 300 μL) in DMF (4 mL). The reaction mixture was stirred at 40° C. overnight, then concentrated under reduced pressure. The residue was taken up in 4:1 dioxane/H_2O, acidified with TFA, and purified by reverse-phase chromatography (20-80% MeCN in H_2O, both containing 0.1% TFA). Lyophilization afforded the title compound as a white solid. H^1 NMR (500 MHz, d_6-DMSO): 8.06 (d, J=6.7 Hz, 2H), 7.88 (m, 1H), 7.75 (d, J=8.5 Hz, 2H), 7.65 (dd, J=3.0, 5.0 Hz, 1H), 7.57 (d, J=4.4 Hz, 1H), 7.50-7.45 (m, 2H), 7.38 (d, J=8.7 Hz, 2H), 7.26 (d, J=8.0 Hz, 1H), 7.05 (m, 1H), 5.55 (s, 2H), 4.04 (t, J=6.6 Hz, 2H), 3.58 (s, 1H), 3.43 (s, 3H), 3.19

(m, 2H), 1.78 (m, 2H), 1.01 (t, J=7.4 Hz, 3H). LC-MS (ESI, Method B): 1.79 min, m/z 565.0 (M+1).

EXAMPLE 19

[0450]



Step A. 5,6-Dichloro-N-[4-(methoxy)phenyl]-1H-benzimidazol-2-amine

[0451] To a solution of 4-anisidine (6.5 mmol, 800 mg) and DIEA (7.2 mmol, 1.24 mL) in CH_2Cl_2 (10 mL) cooled to 0° C. was added thiophosgene (6.5 mmol, 500 μL) dropwise. The solution was allowed to reach ambient temperature for 1 h, and 4,5-dichloro-1,2-phenylenediamine (6.5 mmol, 1.15 g) was added to the reaction. The reaction mixture was heated at 40° C. for 16 h, and MeI (7.2 mmol, 445 μL) and DIEA (7.2 mmol, 1.24 μL) were added. The reaction was heated at 40° C. for 8 h, and allowed to stand at ambient temperature for 16 h. Aqueous workup with CH_2Cl_2/brine, followed by flash chromatography on silica eluting with 4% MeOH in CH_2Cl_2 afforded the product as a brown oil. LC-MS (ESI, Method B): 1.62 min, m/z 308.2 (M+1).

Step B. Methyl 4-[(5,6-dichloro-2-{[4-(methoxy)-phenyl]amino}-1H-benzimidazol-1-yl)methyl]benzoate

[0452] To the title compound of Example 19, Step A (1.3 mmol, 407 mg) in DMF (5 mL) was added NaH (1.6 mmol, 62 mg of 60% suspension in mineral oil). After 10 min methyl-4-(bromomethyl)benzoate (1.3 mmol, 304 mg) was added and the reaction mixture was allowed to stand at ambient temperature for 2 h. Aqueous workup with CH_2Cl_2/saturated $NaHCO_3$ and brine, followed by flash chromatography on silica eluting with 40%, 50% and 60% EtOAc in hexanes afforded the product as a tan solid. LC-MS (ESI, Method B): 1.93 min, m/z 456.1 (M+1).

Step C. Methyl 4-[(5,6-dichloro-2-{[4-(methoxy)-phenyl]imino}-3-methyl-2,3-dihydro-1H-benzimidazol-1-yl)methyl]benzoate

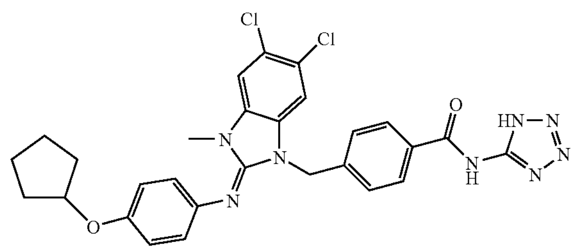
[0453] To a solution of the title compound of Example 19, Step B (0.45 mmol, 203 mg) in DMF (3 mL) was added NaH (0.54 mmol, 21 mg of 60% suspension in mineral oil). After 10 min MeI (0.9 mmol, 56 μL) was added and the reaction was allowed to stand at ambient temperature for 2 h. Aqueous workup with CH_2Cl_2/saturated $NaHCO_3$, followed by flash chromatography on silica eluting with 30% and 40% EtOAc in hexanes, afforded the product as a white solid. LC-MS (ESI, Method B): 1.93 min. m/z 470.2 (M+1).

Step D. Methyl 4-[(5,6-dichloro-2-{[4-(methoxy)-phenyl]imino}-3-methyl-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzamide

[0454] To the title compound of Example 19, Step C (0.02 mmol, 8 mg) dissolved in dioxane (0.8 mL) was added a solution of LiOH (0.42 mmol, 10 mg) in H_2O (0.4 mL). The reaction was stirred at 40° C. for 1 h. The product was partitioned between EtOAc and pH 7 buffer. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure to afford a foam. To the solid was added a solution of 1H-tetraazol-5-amine monohydrate (0.1 mmol, 10 mg), HOBt (0.06 mmol, 9 mg), EDC (0.06 mmol, 11 mg) and DIEA (0.1 mmol, 16 μL) in DMF (0.5 mL). The reaction mixture was heated to 40° C. for 2 h, then concentrated under reduced pressure. Purification by reverse-phase chromatography (10-80% MeCN/H_2O, both containing 0.1% TFA) and lyophilization afforded the title compound as a white solid. 1H NMR (d_6-DMSO+NEt_3, 500 MHz) δ 7.91 (broad d, J=7.8 Hz, 2H), 7.34 (s, 1H), 7.30-7.27 (overlapping s, d, 3H), 6.76 (overlapping m, 4H), 5.08 (s, 2H), 3.71 (s, 3H), 3.11 (s, 3H). LC-MS (ESI, Method A): 2.59 min, m/z 523.1 (M+1).

EXAMPLE 20

[0455]



Step A. Methyl 4-[(5,6-dichloro-2-{[4-(hydroxy)-phenyl]imino}-3-methyl-2,3-dihydro-1H-benzimidazol-1-yl)methyl]benzoate

[0456] To the title compound of Example 19 Step C (0.11 mmol, 50 mg) in CH_2Cl_2 (0.5 mL) cooled to −78° C. was added dropwise BBr_3 (0.33 mol, 330 μL of a 1 M solution in CH_2Cl_2). After addition, the reaction was removed from the cold bath for 30 min, then cooled to −78° C. and diluted with MeOH. The mixture was concentrated under reduced pressure and the product was isolated by chromatography on silica eluting with 4% MeOH in CH_2Cl_2 as a white solid. LC-MS (ESI, Method B): 1.80 min, m/z 456.1 (M+1).

Step B. Methyl 4-[(5,6-dichloro-2-{[4-(cyclopentyloxy)-phenyl]imino}-3-methyl-2,3-dihydro-1H-benzimidazol-1-yl)methyl]benzoate

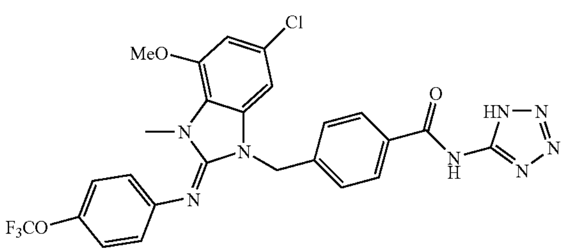
[0457] To the title compound of Example 20, Step A (0.03 mmol, 14 mg) in CH_2Cl_2 (0.6 mL) was added cyclopentanol (0.08 mmol, 7 μL), DIAD (0.06 mmol, 12 μL) and Ph_3P (0.06 mmol, 16 mg). The reaction mixture was allowed to stand at ambient temperature for 16 h, then purified by chromatography on silica eluting with 10% and 25% EtOAc in hexanes to afford the product as a white solid. LC-MS (ESI, Method B): 2.12 min, m/z 524.2 (M+1).

Step C. Methyl 4-[(5,6-dichloro-2-{[4-(cyclopentyloxy)-phenyl]imino}-3-methyl-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzamide

[0458] To the title compound of Example 20, Step B (0.03 mmol, 15 mg) dissolved in dioxane (0.8 mL) was added a solution of LiOH (0.42 mmol, 10 mg) in H_2O (0.4 mL). The reaction was stirred at 40° C. for 1 h, then partitioned between EtOAc and pH 7 buffer. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. To the residue was added a solution of 1H-tetraazol-5-amine monohydrate (0.1 mmol, 10 mg), HOBt (0.06 mmol, 9 mg), EDC (0.06 mmol, 11 mg) and DIEA (0.1 mmol, 16 μL) in DMF (0.5 mL). The reaction mixture was heated to 40° C. for 2 h, then concentrated under reduced pressure. Purification by reverse-phase chromatography (20-60% MeCN in H_2O, both containing 0.1% TFA) and lyophilization afforded the title compound as a white solid. ^{1}H NMR (d_6-DMSO+NEt_3, 500 MHz) δ 7.89 (broad d, J=6.9 Hz, 2H), δ 7.33 (s, 1H), 7.27-7.25 (overlapping s, d, 3H), 6.73 (apparent s, 4H), 5.07 (s, 2H), 4.72 (br m, 1H), 3.12 (s, 3H), 1.86 (br m, 2H), 1.10 (br m, 2H), 1.58 (br m, 2H), δ 1.19 (br m, 2H). LC-MS (ESI, Method A): 3.13 min, m/z 577.3 (M+1).

EXAMPLE 21

[0459]



Step A. 2-Methoxy-6-nitroaniline

[0460] To acetone (60 mL) charged with 2-amino-3-nitrophenol (32 mmol, 4.9 g) and K_2CO_3 (48 mmol, 6.62 g) was added MeI (32 mmol, 1.98 mL). The reaction mixture was stirred rapidly at ambient temperature for 16 h. Acetone was removed under reduced pressure and the residue was partitioned between CH_2Cl_2 and brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to provide the product as a brown solid. LC-MS (ESI, Method C) 2.56 min, m/z 169.1 (M+1).

Step B. 4-Chloro-2-methoxy-6-nitroaniline

[0461] To a solution of the title compound of Example 21, Step A (26.6 mmol, 4.5 g) in MeCN (30 mL) at 60° C. was added N-chlorosuccinimide (29 mmol, 3.9 g). The solution was brought to reflux for 2 h and allowed to stand at ambient temperature for 16 h. The reaction mixture was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic phase was washed with brine, dried with Na_2SO_4, and concentrated in vacuo to afford the product as a brown solid. LC-MS (ESI, Method B): 2.14 min, m/z 203.11 (M+1).

Step C. 4-Chloro-2-methoxy-N-methyl-6-nitroaniline

[0462] To the title compound of Example 21, Step B (19.9 mmol, 4.03 g) in DMF (50 mL) at 0° C. was added portionwise NaH (31.8 mmol, 1.27 g of 60% suspension in mineral oil) (exothermic, gas evolution). After 10 min MeI (23 mmol, 1.5 mL) was added and the reaction was allowed to stand at ambient temperature for 3 h. Saturated $NaHCO_3$ and brine were added to the reaction resulting in formation of a precipitate, which was filtered, washed with water and dried in vacuo. Flash chromatography on silica eluting with 15% EtOAc in hexanes afforded the product as a bright red solid. LC-MS (ESI, Method B): 2.31 min, m/z 217.2 (M+1).

Step D. 5-Chloro-3-methoxy-N^2-methylbenzene-1,2-diamine

[0463] To the title compound in Example 21, Step C (2.3 mmol, 500 mg) in 10% H_2O in DMF (15 naL) was added $SnCl_2.2H_2O$ (9.3 mmol, 2.08 g). The reaction mixture was stirred at 45° C. for 4 h. The reaction mixture was poured into EtOAc and saturated $NaHCO_3$, and the mixture was stirred, affording a yellowish precipitate. The resulting slurry was filtered through celite and the filter cake was washed with water and EtOAc. The organic phase was collected, dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica eluting with 0-7% MeOH in CH_2Cl_2 provided the product as a brown oil. ^{1}H NMR (500 MHz, d_6-DMSO) δ 6.34 (d, J=2.0 Hz, 1H), 6.25 (d, J=2.3 Hz, 1H), 4.93 (s, 2H), 3.73 (s, 3H), 3.51 (br m, 1H), 2.51 (s, 3H). LC-MS (ESI, Method B): 1.27 min, m/z 187.2 (M+1).

Step E. 5-Chloro-7-methoxy-1-methyl-N-[4-(trifluoromethoxy)phenyl]-1H-benzimidazol-2-amine

[0464] A solution of the title compound of Example 21, Step D (0.81 mmol, 151 mg) and 4-trifluoromethoxyphenyl isothiocyanate (0.81 mmol, 132 μL) in CH_2Cl_2 (1 mL) was heated at 45° C. for 2.5 h. The reaction was allowed to cool to ambient temperature and $Hg(O_2CCF_3)_2$ (0.97 mmol, 414 mg), then DMF (1 mL) were added. The reaction mixture was heated at 45° C. for 16 h. CH_2Cl_2 and brine containing Na_2S were added, and the resulting slurry was filtered through celite. The organic phase was collected, dried with $MgSO_4$ and concentrated in vacuo. Flash chromatography on silica eluting with 25% to 40% EtOAc in hexanes afforded the product as a beige solid. ^{1}H NMR (500 MHz, d_6-DMSO) δ 9.11 (s, 1H), 7.91 (d, J=9.2 Hz, 2H), 7.33 (d, J=9.0 Hz, 2H), 7.06 (m, 1H), 6.73 (m, 1H), 3.92 (s, 3H), 3.90 (s, 3H). LC-MS (ESI, Method B): 1.98 min, m/z 372.1 (M+1).

Step F. Methyl 4-[(6-chloro-4-methoxy-3-methyl-2-{[4-(trifluoromethoxy)phenyl]-imino}-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzoate

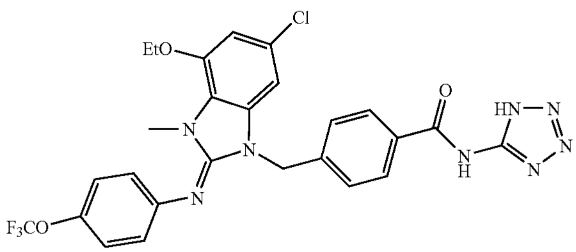
[0465] A solution of the title compound of Example 21, Step E (0.4 mmol, 155 mg) and methyl-4-(bromomethyl-)benzoate (1.6 mmol, 383 mg) in MeCN (2 mL) was heated to 80° C. for 40 h. The reaction was concentrated in vacuo and purified by flash chromatography on silica eluting with CH_2Cl_2, then 2% MeOH in CH_2Cl_2, affording the product as an oil. ^{1}H NMR (500 MHz, d_6-DMSO) δ 7.9 (d, J=8.2 Hz, 2H), 7.28 (d, J=8.2Hz, 2H), 7.10 (d, J=8.7 Hz, 2H), 6.87 (d, J=1.8 Hz, 1H), 6.81-6.86 (overlapping m, 3H), 5.12 (s, 2H), 3.88 (s, 3H), 3.84 (s, 3H). LC-MS (ESI, Method A): 3.19 min, m/z 520.1 (M+1).

Step G. 4-[(6-Chloro-4-methoxy-3-methyl-2-{[4-(trifluoromethoxy)phenyl]-imino}-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzamide

[0466] To the title compound of Example 21, Step F (110 mg, 0.21 mmol) dissolved in dioxane (1 mL) was added a solution of LiOH (25 mg, 1.1 mmol) in H_2O (0.5 mL). The reaction was stirred at 40° C. for 1 h, then partitioned between EtOAc and pH 7 phosphate buffer. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. To the residue was added a solution of 1H-tetraazol-5-amine monohydrate (66 mg, 0.64 mmol), HOBt (65 mg, 0.42 mmol), EDC (81 mg, 0.42 mmol) and DIEA (111 μL, 0.64 mmol) in DMF (0.5 mL). The reaction mixture was heated to 40° C. for 2 h, then concentrated under reduced pressure. Reverse-phase chromatography (20-60% MeCN/H_2O, both containing 0.1% TFA) and lyophilization afforded the title compound as a white solid. ^1H NMR (500 MHz, d_6-DMSO) δ 12.40 (s, 1H), 8.01 (d, J=8.5 Hz, 2H), 7.34 (d, J=8.5 Hz, 2H), 7.36-6.55 (m, 7H), 5.44 (s, 2H), 3.97 (s, 3H), N-Me obscured by H_2O; LCMS (ESI, Method B) 1.66 min, m/z 573.1 (M+1).

EXAMPLE 22

[0467]



Step A. Methyl 4-[(6-chloro-4-hydroxy-3-methyl-2-{[4-(trifluoromethoxy)phenyl]-imino}-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzoate

[0468] To a stirring solution of the title compound of Example 21, Step F (0.12 mmol, 60 mg) in CH_2Cl_2 (0.6 mL) at −78° C. was added dropwise BBr_3 (0.58 mmol, 580 μL of a 1 M solution in CH_2Cl_2). The reaction was removed from the cold bath for 1.5 h, then cooled to −78° C. and quenched by addition of MeOH. The reaction was concentrated in vacuo and purified by flash chromatography on silica eluting with 5% MeOH in CH_2Cl_2 to afford the product as a white solid. LC-MS (ESI, Method B): 2.14 min, m/z 506.2 (M+1).

Step B. Methyl 4-[(6-chloro-4-ethoxy-3-methyl-2-{[4-(trifluoromethoxy)phenyl]-imino}-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzoate

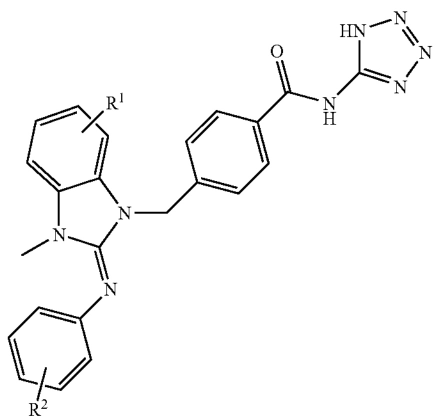
[0469] To the title compound of Example 22, Step A (0.03 mmol, 13 mg) in CH_2Cl_2 (0.6 mL) was added EtOH (0.06 mmol, 6 μL), DIAD (0.06 mmol, 12 μL) and Ph_3P (0.05 mmol, 13 mg). The reaction mixture was allowed to stand at ambient temperature for 4 h, then purified on silica eluting with 10% and 25% EtOAc in hexanes to provide the product as a white solid. LC-MS (ESI, Method A): 3.32 min, m/z 534.1 (M+1).

Step C. 4-[(6-Chloro-4-ethoxy-3-methyl-2-{[4-(trifluoromethoxy)phenyl]-imino}-2,3-dihydro-1H-benzimidazol-1-yl)methyl]-N-1H-tetrazol-5-ylbenzamide

[0470] To the title compound of Example 22, Step B (0.03 mmol, 13 mg) dissolved in dioxane (1 mL) was added a solution of LiOH (0.4 mmol, 10 mg) in H_2O (0.5 mL). The reaction mixture was stirred at 40° C. for 1 h, then partitioned between EtOAc and pH 7 buffer. The organic phase was dried with $MgSO_4$ and concentrated under reduced pressure. To the residue was added a solution of 1H-tetraazol-5-amine monohydrate (0.1 mmol, 10 mg), HOBt (0.06 mmol, 9 mg), EDC (0.06 mmol, 11 mg) and DIEA (0.1 mmol, 16 μL) in DMF (0.5 mL). The solution was heated to 40° C. for 2 h, then concentrated under reduced pressure. Purification by reverse-phase chromatography (20-60% MeCN in H_2O, both containing 0.1% TFA) and lyophilization afforded the title compound as a white solid. ^1H NMR (d_6-DMSO+NEt_3, 500 MHz) δ 7.89 (broad d, J=6.5 Hz, 2H), 7.25 (d, J=8.2 Hz, 2H), 7.12 (d, J=8.3 Hz, 2H), 6.88-6.86 (overlapping s, m, 3H), 6.80 (s, 1H), 5.11 (s, 2H), 4.14 (q, J=6.9 Hz, 2H), 1.36 (t, J=6.9 Hz, 3H), N-Me obscured by H_2O peak. LC-MS (ESI, Method A): 2.95 min, m/z 587.0 (M+1).

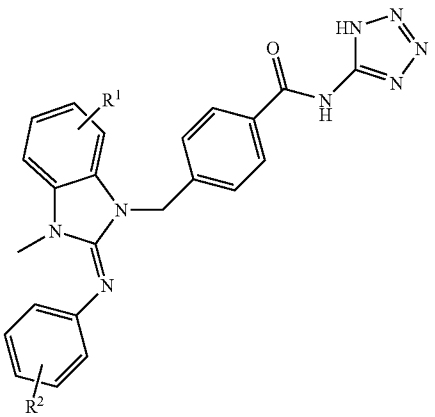
[0471] Following the procedures outlined for Examples 1-22 the compounds listed in Tables 1-4 were prepared

TABLE 1



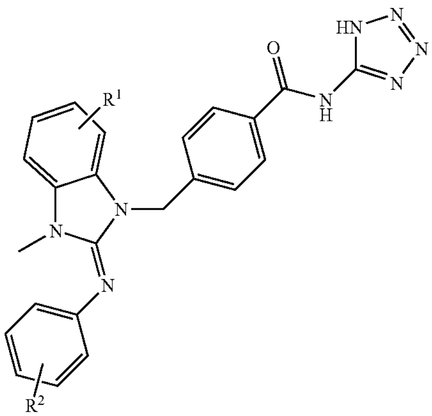
Example	R^1	R^2	LCMS data; retention time (min)/M + H	Prepared according to example no.
23	H	3,5-diCl	Method A 2.59 min/493.0 (M + 1)	Ex 4
24	6-MeO	3,5-diCl	Method A 2.68 min/523.1 (M + 1)	Ex 4
25	H	4-(1'-cyclohexenyl)	Method C 2.74 min/505.2 (M + 1)	Ex 4
26	6-CF_3O	4-CF_3O	Method C 2.72 min/593.1 (M + 1)	Ex 4
27	6-CF_3	4-CF_3O	Method C 2.79 min/577.1 (M + 1)	Ex 5
28	4,6-diCl	4-CF_3O	Method A 2.88 min/577.1 (M + 1)	Ex 5
29	6-CF_3	4-Cl	Method C 2.56 min/527.2 (M + 1)	Ex 12
30	6-PrO	4-CF_3O	Method C 2.66 min/567.2 (M + 1)	Ex 5

TABLE 1-continued



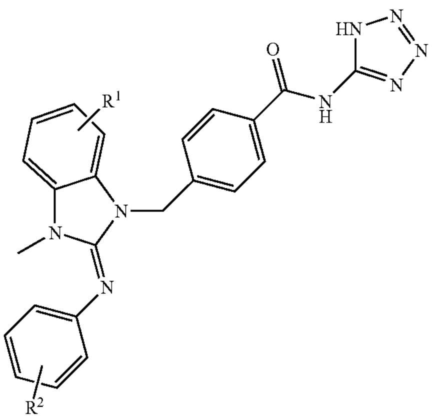
Example	R^1	R^2	LCMS data; retention time (min)/M + H	Prepared according to example no.
31	6-CF_3	3-CF_3	Method C 2.94 min/561.2 (M + 1)	Ex 13
32	6-CF_3	4-CF_3	Method C 3.01 min/561.2 (M + 1)	Ex 13
33	4-Cl, 6-CF_3	4-CF_3O	Method C 3.56 min/611.2 (M + 1)	Ex 7
34	5,6-diCl	4-cPentCH_2O	Method A 3.23 min/591.3 (M + 1)	Ex 20
35	5,6-diCl	4-^{i}PrO	Method A 2.99 min/551.2 (M + 1)	Ex 20
36	5,6-diCl	4-BnO	Method A 2.90 min/599.1 (M + 1)	Ex 20
37	5,6-diCl	4-^{t}Bu	Method C 2.87 min/549.2 (M + 1)	Ex 13
38	5,6-diCl	4-CF_3	Method C 3.14 min/561.2 (M + 1)	Ex 13
39	6-MeO	4-(3',3',5',5'-tetramethylcyclohexyl	Method B 3.2 min./593.4 (M + 1)	Ex 4
40	6-MeO	4-(4',4'-difluoro-cyclohexyl)	Method B 1.86 min/573.3 (M + 1)	Ex 4
41	5-PrO	4-CF_3CH_2O	Method A 3.07 min/581.1 (M + 1)	Ex 6
42	4-BuO, 6-Cl	4-CF_3O	Method A 3.32 min/615.0 (M + 1)	Ex 22
43	5,6-diCl	3,4-diCl	Method B 1.92 min/562.9 (M + 3)	Ex 13
44	4,6-diCF_3	4-CF_3O	Method A 3.94 min/615.0 (M + 1)	Ex 7
45	6-CF_3	4-(3',3',5',5'-tetramethylcyclohexyl)	Method C 3.59 min/631.4 (M + 1)	Ex 4
46	6-MeO	4-(1'-adamantyl)	Method C 3.19 min/589.4 (M + 1)	Ex 4

TABLE 1-continued



Example	R^1	R^2	LCMS data; retention time (min)/M + H	Prepared according to example no.
47	4-MeO, 6-Cl	4-cyclohexyl	Method C 3.09 min/571.3 (M + 1)	Ex 4
48	5-PrO	4-CF_2HCH_2	Method B 2.08 min/547 (M + 1)	Ex 6
49	6-CF_3	4-Bu	Method B 2.08 min/549.4 (M + 1)	Ex 6
50	4-Et, 6-CF_3	4-^{t}Bu	Method A 3.11 min/577.2 (M + 1)	Ex 21
51	4-Et, 6-CF_3	4-F	Method A 2.78/539.1 (M + 1)	Ex 21
52	4-PrO, 6-Cl	4-CF_3O	Method A 3.07 min/601.03 (M + 1)	Ex 22
53	4-^{i}PrO, 6-Cl	4-CF_3O	Method A 3.04 min/601.0 (M + 1)	Ex 22
54	4-Ph, 6-CF_3	4-CF_3O	Method A 3.17 min/653.3 (M + 1)	Ex 7
55	4-MeO, 6-Cl	tBu	Method A 2.99 min/545.2 (M + 1)	Ex 21
56	6-CF_3	4-(3',5'-dimethylcyclopentyl)	Method C 3.46 min/589.4 (M + 1)	Ex 6
57	6-MeO	4-(3',5'-dimethylcyclopentyl)	Method C 3.30 min/551.4 (M + 1)	Ex 4
58	4-Et, 6-CF_3	4-Me	Method A 2.88 min/535.3 (M + 1)	Ex 21
59	4-Et, 6-CF_3	4-^{i}Pr	Method A 3.04 min/563.3 (M + 1)	Ex 21
60	4-BuO, 6-CF_3	4-CF_3O	Method A 3.26 min/649.0 (M + 1)	Ex 21
61	6-F	4-cyclohexyl	Method C 3.53 min/525.3 (M + 1)	Ex 6

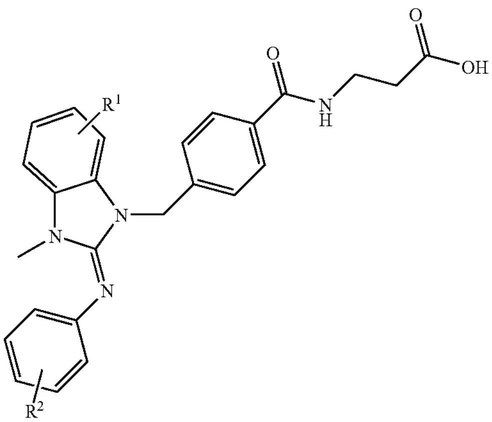
TABLE 1-continued



Example	R^1	R^2	LCMS data; retention time (min)/M + H	Prepared according to example no.
62	4-MeO, 6-Cl	3-Cl, 4-CF_3O	Method A 2.91 min/606.9 (M + 1)	Ex 21
63	4-OH, 6-Cl	4-CF_3O	Method A 2.70 min/559.0 (M + 1)	Ex 22
64	4-MeO, 6-CF_3	4-CF_3O	Method C 3.14 min/607.3 (M + 1)	Ex 21
65	4-PrO, 6-CF_3	4-CF_3O	Method C 3.71 min/657.2 (M + 1)	Ex 21
66	6-MeO	3-Me, 4-^{i}Pr	Method C 2.99 min/511.3 (M + 1)	Ex 6
67	6-CF_3	3-Me, 4-^{i}Pr	Method C 3.17 min/549.3 (M + 1)	Ex 6
68	4-MeO, 6-CF_3	4-^{t}Bu	Method B 2.04 min/579.2 (M + 1)	Ex 21
69	4-PrO, 6-CF_3	4-^{t}Bu	Method B 2.22 min/607.3 (M + 1)	Ex 21
70	4-PrO	4-CF_3O	Method A 2.99 min/567.0 (M + 1)	Ex 21
71	4-EtO, 6-CF_3	4-CF_3O	Method A 3.00 min/621.0 (M + 1)	Ex 21

[0472]

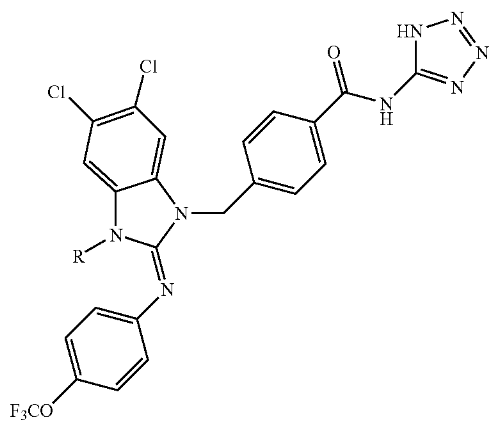
TABLE 2



Example	R^1	R^2	LCMS data: retention time (min)/M + H	Prepared according to example no.
72	6-MeO	3,5-diCl	Method A 2.61 min/527.2 (M + 1)	Ex 4
73	5-Cl	4-CF_3O	Method C 2.48 min/547.1 (M + 1)	Ex 12
74	5,6-diCl	4-cyclo-hexyl	Method C 2.86 min/579.2 (M + 1)	Ex 4
75	6-CF_3	4-Cl	Method C 2.50 min/531.1 (M + 1)	Ex 13
76	6-CF_3	3-CF_3	Method C 2.78 min/565.2 (M + 1)	Ex 13
77	6-CF_3	4-CF_3	Method C 2.85 min/565.2 (M + 1)	Ex 13
78	4-PrO	4-CF_3O	Method A 2.84 min/571.1 (M + 1)	Ex 21

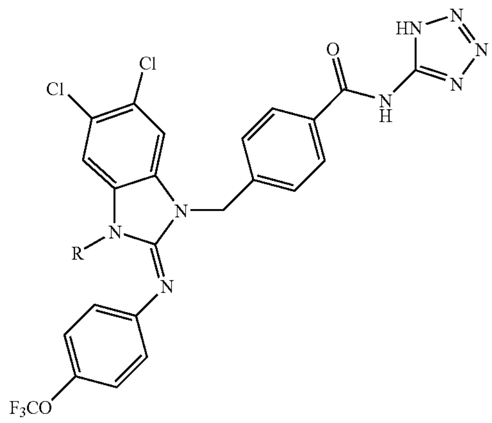
[0473]

TABLE 3



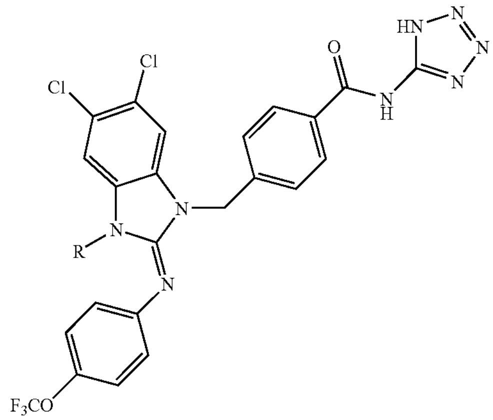
Example	R	LCMS data: retention time (min)/M + H	Prepared according to example no.
79	Et	Method A 2.88 min/591.1 (M + 1)	Ex 3
80	Pr	Method A 3.24 min/605.1 (M + 1)	Ex 3

TABLE 3-continued



Example	R	LCMS data: retention time (min)/M + H	Prepared according to example no.
81	Bn	Method A 3.34 min/652.9 (M + 1)	Ex 3
82	^{i}Pr	Method A 2.92 min/605.1 (M + 1)	Ex 3
83	FCH_2CH_2	Method A 2.86 min/608.9 (M + 1)	Ex 3
84	$Me_2NCH_2CH_2$	Method A 2.74 min/634.3 (M + 1)	Ex 3
85	$MeOCH_2CH_2$	Method A 2.94 min/621.0 (M + 1)	Ex 7

TABLE 3-continued



Example	R	LCMS data: retention time (min)/M + H	Prepared according to example no.
86	$MeOCH_2CH_2CH_2$	Method A 2.95 min/634.9 (M + 1)	Ex 7
87	$Me_2NCH_2CH_2CH_2$	Method A 2.46 min/647.9 (M + 1)	Ex 7

[0474]

TABLE 4

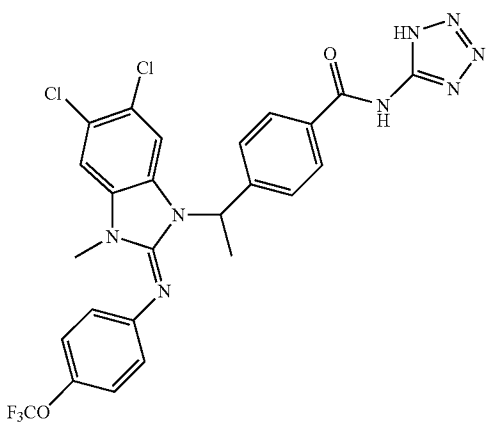
Example	R^2	LCMS data: retention time (min)/M + H	Prepared according to example no.
88		Method A 2.66 min/647.9 (M + 1)	Ex 3

TABLE 4-continued

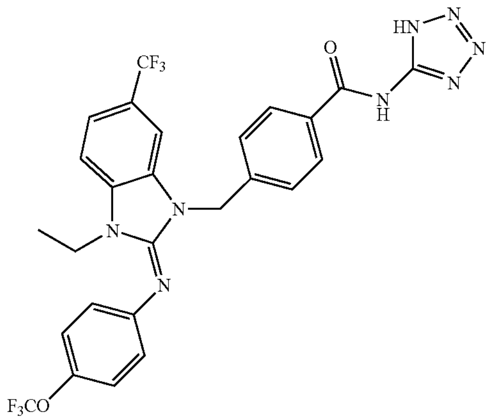
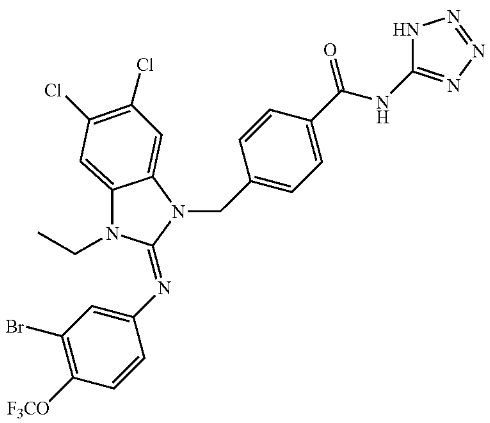
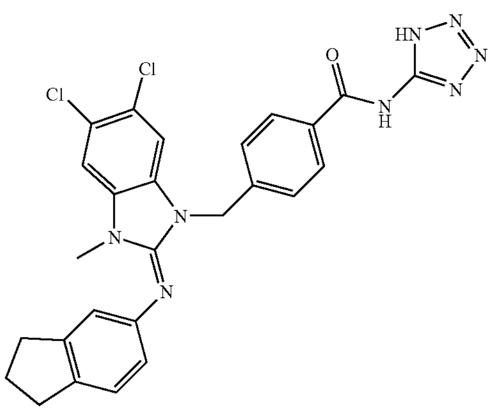
Example	R^2	LCMS data: retention time (min)/M + H	Prepared according to example no.
89		Method C 2.99 min/591.3 (M + 1)	Ex 13
90		Method C 3.75 min/673.1 (M + 1)	Ex 3
91		Method C 2.67 min/533.2 (M + 1)	Ex 13

TABLE 4-continued

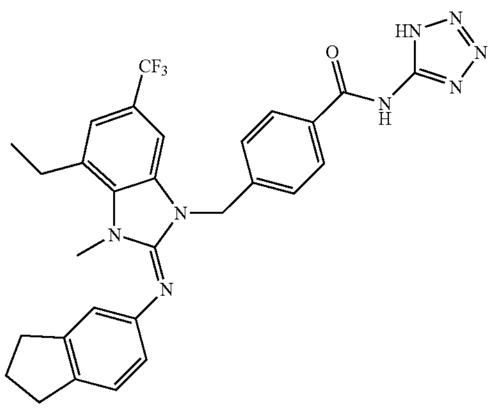
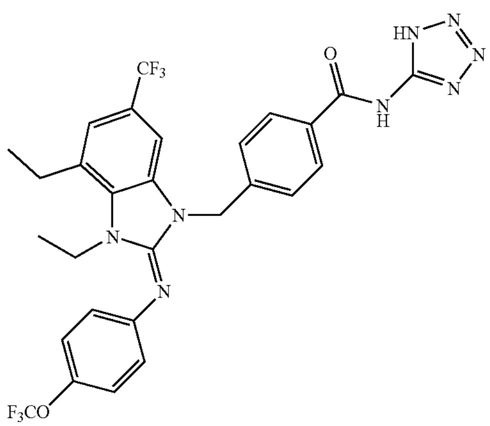
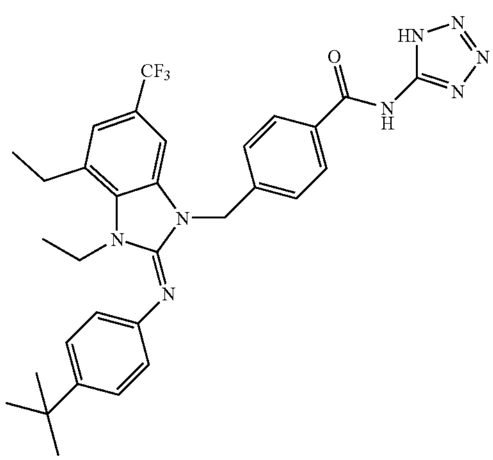
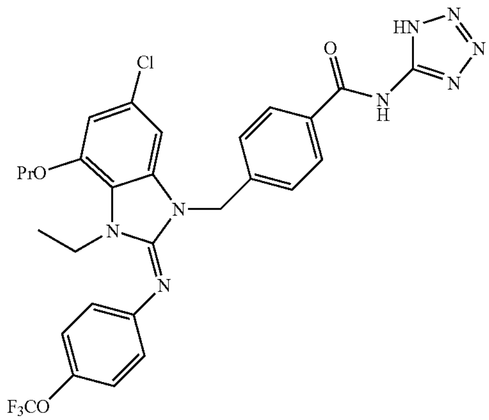
Example	R^2	LCMS data: retention time (min)/M + H	Prepared according to example no.
92		Method A 2.96 min/561.3 (M + 1)	Ex 21
93		Method A 3.00 min/605.3 (M + 1)	Ex 21
94		Method A 3.10 min/577.7 (M + 1)	Ex 21

TABLE 4-continued

Example	R^2	LCMS data: retention time (min)/M + H	Prepared according to example no.
95		Method A 3.12 min/615.0 (M + 1)	Ex 21

Biological Assays

[0475] The ability of the compounds of the present invention to inhibit the binding of glucagon and their utility in treating or preventing type 2 diabetes mellitus and the related conditions can be demonstrated by the following in vitro assays.

Glucagon Receptor Binding Assay

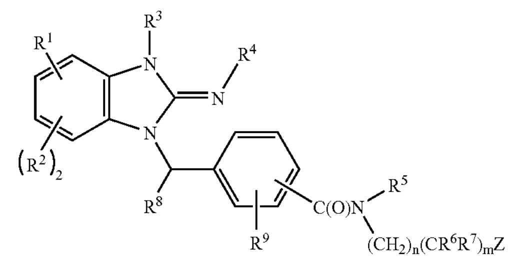
[0476] A stable CHO (Chinese hamster ovary) cell line expressing cloned human glucagon receptor was maintained as described (Chicchi et al. *J Biol Chem* 272, 7765-9 (1997); Cascieri et al. *J Biol Chem* 274, 8694-7 (1999)). To determine antagonistic binding affinity of compounds 0.002 mg of cell membranes from these cells were incubated with ^{125}I-Glucagon (New England Nuclear, MA) in a buffer containing 50 mM Tris-HCl (pH 7.5), 5 mM $MgCl_2$, 2 mM EDTA, 12% Glycerol, and 0.200 mg WGA coated PVT SPA beads (Amersham), +/−compounds or 0.001 mM unlabeled glucagon. After 4-12 hours incubation at room temperature, the radioactivity bound to the cell membranes was determined in a radioactive emission detection counter (Wallac-Microbeta). Data was analyzed using the software program Prism® from GraphPad. The IC_{50} were calculated using non-linear regression analysis assuming single site competition.

Inhibition of Glucagon-Stimulated Intracellular cAMP Formation

[0477] Exponentially growing CHO cells expressing human glucagon receptor were harvested with the aid of enzyme-free dissociation media (Specialty Media), pelleted at low speed, and re-suspended in the Cell Stimulation Buffer included in the Flash Plate cAMP kit (New England Nuclear, SMP0004A). The adenylate cyclase assay was setup as per manufacturer instructions. Briefly, compounds were diluted from stocks in DMSO and added to cells at a final DMSO concentration of 5%. Cells prepared as above were preincubated in flash plates coated with anti-cAMP antibodies (NEN) in presence of compounds or DMSO controls for 30 minutes, and then stimulated with glucagon (250 pM) for an additional 30 minutes. The cell stimulation was stopped by addition of equal amount of a detection buffer containing lysis buffer as well as ^{125}I-labeled cAMP tracer (NEN). After 3 hours of incubation at room temperature the bound radioactivity was determined in a liquid scintillation counter (TopCount-Packard Instruments). Basal activity (100% inhibition) was determined using the DMSO control while 0% inhibition was defined at the amount of pmol cAMP produced by 250pM glucagon.

[0478] Certain embodiments of the invention has been described in detail; however, numerous other embodiments are contemplated as falling within the invention. Thus, the claims are not limited to the specific embodiments described herein. All patents, patent applications and publications that are cited herein are hereby incorporated by reference in their entirety.

1. A compound represented by formula I:



I

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 represents H or is independently selected from the group consisting of:

a) OH, halo, CO_2R^a, $C(O)NR^bR^c$, NR^bR^c, CN or $S(O)_pR^d$;

b) C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, OC_{1-10}alkyl, OC_{3-10}alkenyl and OC_{3-10}alkynyl, said groups being optionally substituted with:

(1) 1-5 halo groups up to a perhaloalkyl group;

(2) 1 oxo group;

(3) 1-2 OH groups;

(4) 1-2 C_{1-10}alkoxy groups, each optionally substituted with: up to five halo or a perhaloalkoxy, 1 OH or CO^2R^a group;

(5) 1 CO_2R^a or $S(O)_pR^d$;

(6) 1-2 Aryl, Hetcy or HAR groups, each optionally substituted as follows:

(a) 1-5 halo groups,

(b) 1 OH, CO_2R^a, CN, $S(O)_pR^d$, NO_2 or $C(O)NR^bR^c$,

(c) 1-2 C_{1-10}alkyl or alkoxy groups, each optionally substituted with: 1-5 halo, up to perhaloalkyl, and 1-2 OH or CO_2R^a groups; and

(d) 1-2 phenyl rings, each of which is optionally substituted as follows: 1-5 halo groups up to perhalo, 1-3 C_{1-10}alkyl or alkoxy groups, each being further optionally substituted with 1-5 halo up to perhalo, or 1-2 hydroxy or CO_2R^a groups;

c) Aryl, HAR, Hetcy, —O-Aryl, —O-HAR and —O-Hetcy, each optionally substituted as set forth below:

(1) 1-3 C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl groups optionally substituted with 1-5 halo groups; 1-2 OH groups; phenyl optionally substituted with 1-3 halo, C_{1-6}alkyl or C_{1-6}alkoxy groups, the alkyl and alkoxy groups being further optionally substituted with 1-3 halo groups; CO_2R^a; CN or $S(O)_pR^d$ groups; and

(2) 1-3 C_{1-10}alkoxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups, 1-2 OH; phenyl optionally substituted with 1-3 halo, C_{1-6}alkyl or C_{1-6}alkoxy groups, the alkyl and alkoxy groups being further optionally substituted with 1-3 halo groups; CO_2R^a; CN or $S(O)_pR^d$ groups;

said Aryl, HAR, Hetcy —O-Aryl, —O-HAR and —O-Hetcy group c) being further optionally substituted on carbon by a group selected from the group consisting of;

(3) 1-5 halo groups;

(4) 1-2 OH groups;

(5) 1 $S(O)_pR^d$, NO_2 or CN group;

(6) 1-2 CO_2R^a;

(7) —$C(O)NR^bR^c$;

each R^2 represents H or is independently selected from the group consisting of:

a) OH, halo, CO_2R^a, $C(O)NR^bR^c$, NR^bR^c, CN or $S(O)_pR^d$;

b) C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, OC_{1-10}alkyl, OC_{3-10}alkenyl and OC_{3-10}alkynyl, said groups being optionally substituted with:

(1) 1-5 halo groups up to a perhaloalkyl group;

(2) 1 oxo group;

(3) 1 OH group;

(4) 1 C_{1-10}alkoxy group, each optionally substituted with: up to five halo or a perhaloalkoxy, 1 OH or CO^2R^a group;

(5) 1 CO_2R^a or $S(O)_pR^d$;

(6) 1 Aryl, Hetcy or HAR group, each optionally substituted as follows:

(a) 1-5 halo groups,

(b) 1 OH, CO_2R^a, CN, $S(O)_pR^d$, NO_2 or $C(O)NR^bR^c$,

(c) 1-2 C_{1-10}alkyl or alkoxy groups, each optionally substituted with: 1-5 halo, up to perhaloalkyl, and 1-2 OH or CO_2R^a groups; and

(d) 1-2 phenyl rings, each of which is optionally substituted as follows: 1-5 halo groups up to perhalo; 1-3 C_{1-10}alkyl or alkoxy groups, each being further optionally substituted with 1-5 halo up to perhalo; and 1-2 hydroxy or CO_2R^a groups;

c) Aryl, HAR, Hetcy, —O-Aryl, —O-HAR and —O-Hetcy, each optionally substituted as set forth below:

(1) 1-3 C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl groups optionally substituted with 1-5 halo groups, 1-2 OH, phenyl, CO_2R^a, CN or $S(O)_pR^d$ groups;

(2) 1-3 C_{1-10}alkoxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups, 1-2 OH, phenyl, CO_2R^a, CN or $S(O)_pR^d$ groups;

said Aryl, HAR or Hetcy group c) being further optionally substituted on carbon by a group selected from the group consisting of;

(3) 1-5 halo groups up to perhalo;

(4) 1 OH group;

(5) 1 $S(O)_pR^d$, NO_2 or CN group;

(6) 1 CO_2R^a;

R^3 is selected from the group consisting of:

a) C_{1-10}alkyl or C_{2-10}alkenyl, each optionally substituted with

1-5 halo groups up to perhalo;

1-2 OH, C_{1-3}alkoxy or haloC_{1-3}alkoxy groups;

1-2 NR^cR^d groups; and

1-2 Aryl, HAR or Hetcy groups, each optionally substituted with 1-3 halo groups and 1-2 groups selected from CN, NO_2, C_{1-3}alkyl, haloC_{1-3}alkyl, C_{1-3}alkoxy and haloC_{1-3}alkoxy groups,

b) Aryl, HAR or Hetcy, each optionally substituted with 1-3 halo groups and 1-2 groups selected from CN, NO_2, C_{1-3}alkyl, haloC_{1-3}alkyl, C_{1-3}alkoxy and haloC_{1-3}alkoxy groups;

R^4 is independently selected from the group consisting of: Aryl, HAR or Hetcy, each optionally substituted as set forth below:

(1) 1-3 C_{1-14}alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl groups optionally substituted with 1-5 halo groups, 1-2 OH, CO_2R^a, CN or $S(O)_pR^d$ groups or phenyl optionally substituted as follows: 1-5 halo groups up to perhalo; 1-3 C_{1-10}alkyl or alkoxy groups, each being further

optionally substituted with 1-5 halo up to perhalo, or 1-2 hydroxy or CO_2R^a groups;

(2) 1-3 C_{1-10}alkoxy or C_{3-10}alkenyloxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups, 1-2 OH, CO_2R^a, CN, $S(O)_pR^d$, and phenyl optionally substituted as follows: 1-5 halo groups up to perhalo; 1-3 C_{1-10}alkyl or alkoxy groups, each being further optionally substituted with 1-5 halo up to perhalo, or 1-2 hydroxy or CO_2R^a groups;

(3) 1-2 Aryl, HAR or Hetcy, OAryl, OHAR or OHetcy groups, each optionally substituted as follows:

(i) 1-3 halo groups;

(ii) 1-2 C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-10}alkynyl groups each optionally substituted with 1-5 halo groups, 1-2 OH, phenyl, CO_2R^a, CN or $S(O)_pR^d$ groups;

(iii) 1-2 C_{1-10}alkoxy groups the alkyl portion of which being optionally substituted with 1-5 halo groups, 1-2 OH, phenyl, CO_2R^a, CN or $S(O)_pR^d$ groups; and

(iv) 1-2 CO_2R^a, $S(O)_pR^d$, CN, NR^bR^c, NO_2 or OH groups;

said Aryl, HAR or Hetcy group R^4 being further optionally substituted on carbon by a group selected from the group consisting of;

(4) 1-5 halo groups;

(5) 1-2 OH groups;

(6) 1 $S(O)_pR^d$, NO_2 or CN group;

(7) 1-2 CO_2R^a;

R^5 represents H or C_{1-6}alkyl;

R^6 is selected from the group consisting of H, OH, F or C_{1-3}alkyl;

R^7 is H or F, or R^6 and R^7 are taken in combination and represent oxo;

R^8 represents H or C_{1-6}alkyl, optionally substituted with OH and 1-5 halo groups up to perhalo;

R^9 represents H, halo, OH, C_{1-6}alkyl, optionally substituted with 1-5 halo groups up to perhalo, or C_{1-6}alkoxy, optionally substituted with 1-3 halo groups up to perhalo,

or when R^9 is ortho to the benzylic group, R^8 and R^9 can be taken together and represent a —$(CH_2)_{2-4}$— or a —O—$(CH_2)_{1-3}$— group;

R^a is H or C_{1-10}alkyl, optionally substituted with phenyl, OH, OC_{1-6}alkyl, CO_2H, CO_2C_{1-6}alkyl and 1-3 halo groups;

R^b is H or C_{1-10}alkyl;

R^c is H or is independently selected from:

(a) C_{1-10}alkyl, optionally substituted with OH, OC_{1-6}alkyl, CO_2H, CO_2C_{1-6}alkyl, and 1-3 halo groups;

(b) Aryl or Ar—C_{1-6}alkyl, each optionally substituted with 1-5 halos and 1-3 members selected from the group consisting of: CN, OH, C_{1-10}alkyl and OC_{1-10}alkyl, said alkyl and alkoxy being further optionally substituted with 1-5 halo groups up to perhalo;

(c) Hetcy or Hetcy-C_{1-6}alkyl, optionally substituted with 1-5 halo groups and 1-3 groups selected from: oxo, C_{1-10}alkyl and OC_{1-10}alkyl, said alkyl and alkoxy being further optionally substituted with 1-5 halo groups up to perhalo; and

(d) HAR or HAR-C_{1-6}alkyl, optionally substituted with 1-5 halo groups and 1-3 groups selected from: C_{1-10}alkyl and OC_{1-10}alkyl, said alkyl and alkoxy being further optionally substituted with 1-5 halo groups up to perhalo;

R^d is C_{1-10}alkyl, Aryl or Ar—C_{1-10}alkyl;

m is an integer selected from 0, 1 and 2;

n is an integer selected from 0 to 6;

p is an integer selected from 0, 1 and 2, and

when at least one of m and n is other than 0, Z is selected from CO_2R^a, 5-tetrazolyl and 5-(2-oxo-1,3,4-oxadiazolyl), and when both m and n are 0, Z is selected from 5-tetrazolyl and 5-(2-oxo-1,3,4-oxadiazolyl).

2. A compound in accordance with claim 1 wherein R^1 is selected from the group consisting of: H, halo, C_{1-10}alkyl and OC_{1-10}alkyl, said alkyl and O-alkyl groups being optionally substituted with 1-5 halo groups up to a perhaloalkyl or perhaloalkoxy.

3. A compound in accordance with claim 2 wherein R^1 is selected from the group consisting of: H, halo, C1-4alkyl, C1-4alkoxy, said alkyl and alkoxy being optionally substituted with 1-3 halo groups.

4. A compound in accordance with claim 1 wherein each R^2 represents H or is independently selected from the group consisting of:

a) halo or $S(O)_pR^d$; wherein p is 2 and R^d represents C_{1-10}alkyl;

b) C_{1-10}alkyl, C_{2-10}alkenyl, OC_{1-10}alkyl and OC_{3-10}alkenyl, said groups being optionally substituted with:

(1) 1-5 halo groups up to a perhaloalkyl group;

(2) 1 C_{1-10}alkoxy group, each optionally substituted with: up to five halo or perhaloalkoxy, 1 OH or CO^2R^a group;

(3) 1 Aryl or HAR group, each optionally substituted as follows:

(a) 1-5 halo groups,

(b) 1-2 C_{1-10}alkyl or alkoxy groups, each optionally substituted with: 1-5 halo, up to perhaloalkyl, and 1-2 OH or CO_2R^a groups;

c) Aryl or HAR, each optionally substituted with:

(1) 1-2 C_{1-10}alkyl groups optionally substituted with 1-5 halo groups;

(2) 1-2 C_{1-10}alkoxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups;

said Aryl or HAR being further optionally substituted on carbon by 1-3 halo groups; up to perhalo.

5. A compound in accordance with claim 4 wherein one R^2 group represents H and the other represents H or is selected from the group consisting of:

a) halo or $S(O)_pR^d$; wherein p is 2 and R^d represents C_{1-10}alkyl;

b) C_{1-10}alkyl, C_{2-10}alkenyl, OC_{1-10}alkyl or OC_{3-10}alkenyl, said groups being optionally substituted with:

(1) 1-5 halo groups up to a perhaloalkyl group;

(2) 1 C_{1-10}alkoxy group, each optionally substituted with: up to five halo or a perhaloalkoxy, 1 OH or CO^2R^a group;

(3) 1 Aryl or HAR group, each optionally substituted as follows:

(a) 1-5 halo groups,

(b) 1-2 C_{1-10}alkyl or alkoxy groups, each optionally substituted with: 1-5 halo, up to perhaloalkyl, and 1-2 OH or CO_2R^a groups;

c) Aryl or HAR, each optionally substituted with:

(1) 1-2 C_{1-10}alkyl groups optionally substituted with 1-5 halo groups;

(2) 1-2 C_{1-10}alkoxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups;

said Aryl or HAR being further optionally substituted on carbon by 1-3 halo groups; up to perhalo. Within this subset, all other variables are as originally defined with respect to formula I.

6. A compound in accordance with claim 5 wherein:

one R^2 group represents H and the other represents H or a member selected from the group consisting of:

a) halo or $S(O)_pR^d$; wherein p is 2 and R^d represents C_{1-2}alkyl;

b) C_{1-4}alkyl, C_{2-4}alkenyl, OC_{1-4}alkyl or OC_{3-4}alkenyl, said groups being optionally substituted with:

(1) 1-5 halo groups up to a perhaloalkyl group;

(2) 1 Cl_4alkoxy group, optionally substituted with: up to 3 halo or a perhaloalkoxy group;

(3) 1 Aryl or HAR group, each optionally substituted as follows:

(a) 1-3 halo groups,

(b) 1 C_{1-4}alkyl or alkoxy group, each optionally substituted with: 1-3 halo, up to perhaloalkyl, groups;

c) Aryl or HAR, each optionally substituted with:

(1) 1-2 C_{1-4}alkyl groups optionally substituted with 1-3 halo groups;

(2) 1-2 C_{1-4}alkoxy groups, the alkyl portion of which is optionally substituted with 1-3 halo groups;

said Aryl or HAR being further optionally substituted on carbon by 1-3 halo groups; up to perhalo.

7. A compound in accordance with claim 1 wherein R^3 is selected from the group consisting of:

a) C_{1-6}alkyl optionally substituted with:

1-3 halo groups up to perhalo;

1OH, C, $_3$alkoxy or haloC_{1-3}alkoxy group;

$1NR^cR^d$ group; and

1 Aryl or HAR group, each optionally substituted with 1-3 halo groups and 1-2 groups selected from C_{1-3}alkyl, haloC_{1-3}alkyl, C_{1-3}alkoxy and haloC_{1-3}alkoxy groups,

b) Aryl or HAR, each optionally substituted with 1-3 halo groups and 1-2 groups selected from C_{1-3}alkyl, haloC_{1-3}alkyl, C_{1-3}alkoxy and haloC_{1-3}alkoxy groups.

8. A compound in accordance with claim 7 wherein R^3 is selected from the group consisting of:

a) C_{1-6}alkyl optionally substituted with:

1-3 halo groups up to perhalo;

$1C_{1-3}$alkoxy or haloC_{1-3}alkoxy group;

$1NR^cR^d$ group; wherein R^c and R^d are independently selected from H, C_{1-3}alkyl and phenyl; and

1 Aryl or HAR group, each optionally substituted with 1-3 halo groups and 1-2 groups selected from C_{1-3}alkyl, haloC_{1-3}alkyl, C_{1-3}alkoxy and haloC_{1-3}alkoxy groups,

b) Aryl or HAR, each optionally substituted with 1-3 halo groups and 1 group selected from: C_{1-3}alkyl, haloC_{1-3}alkyl, C_{1-3}alkoxy and haloC_{1-3}alkoxy.

9. A compound in accordance with claim 1 wherein:

R^4 represents an Aryl or HAR group, each optionally substituted as set forth below:

(1) 1-2 C_{1-10}alkyl or C_{2-10}alkenyl groups, which are optionally substituted with 1-3 halo groups, or phenyl optionally substituted with 1-2 halo, C_{1-4}alkyl or alkoxy groups, each being further optionally substituted with 1-3 halo groups;

(2) 1-2 C_{1-10}alkoxy or C_{3-10}alkenyloxy groups, which are optionally substituted with 1-3 halo groups, 1-2 OH or $S(O)_pR^d$, and phenyl optionally substituted as follows: 1-3 halo groups up to perhalo; 1-2 C_{1-6}alkyl or alkoxy groups, each being further optionally substituted with 1-3 halo up to perhalo, or 1-2 hydroxy or CO_2R^a groups;

(3) 1-2 Aryl, HAR or Hetcy, OAryl, OHAR or OHetcy groups, each optionally substituted as follows:

(i) 1-3 halo groups;

(ii) 1-2 C_{1-3}alkyl or C_{2-4}alkenyl groups each optionally substituted with 1-3 halo groups, and 1 of OH, phenyl, CO_2R^a, CN and $S(O)_pR^d$;

(iii) 1-2 C_{1-3}alkoxy groups the alkyl portion of which being optionally substituted with 1-3 halo groups, and 1 of OH, phenyl, CO_2R^a, CN or $S(O)_pR^d$; and

(iv) 1-2 CO_2R^a, $S(O)_pR^d$, CN, NR^bR^c, NO_2 or OH groups;

said Aryl, HAR or Hetcy group R^4 being further optionally substituted on carbon by a group selected from the group consisting of;

(4) 1-5 halo groups;

(5) 1-2 OH groups;

(6) 1 $S(O)_pR^d$, NO_2 or CN group.

10. A compound in accordance with claim 1 wherein R^5 represents H or CH_3.

11. A compound in accordance with claim 1 wherein R^8 is selected from the group consisting of H and C_{1-3}alkyl.

12. A compound in accordance with claim 1 wherein R^6 and R^7 represent H.

13. A compound in accordance with claim 9 wherein R^9 represents H.

14. A compound in accordance with claim 1 wherein m is 0 and n is an integer selected from 0 to 2.

15. A compound in accordance with claim 1 wherein when n is 1 or 2, Z is selected from CO_2R^a and 5-tetrazolyl, when both m and n are 0, Z is 5-tetrazolyl.

16. A compound in accordance with claim 1 wherein:

R^1 is selected from the group consisting of: H, halo, C_{1-10}alkyl and OC_{1-10}alkyl, said alkyl and O-alkyl groups being optionally substituted with 1-5 halo groups up to a perhaloalkyl or perhaloalkoxy;

each R^2 represents H or is independently selected from the group consisting of:

a) halo or $S(O)_pR^d$; wherein p is 2 and R^d represents C_{1-10}alkyl;

b) C_{1-10}alkyl, C_{2-10}alkenyl, OC_{1-10}alkyl and OC_{3-10}alkenyl, said groups being optionally substituted with:

(1) 1-5 halo groups up to perhaloalkyl;

(2) 1 C_{1-10}alkoxy group, each optionally substituted with: up to five halo or perhaloalkoxy, 1 OH or CO^2R^a group;

(3) 1 Aryl or HAR group, each optionally substituted as follows:

(a) 1-5 halo groups,

(b) 1-2 C_{1-10}alkyl or alkoxy groups, each optionally substituted with: 1-5 halo, up to perhaloalkyl, and 1-2 OH or CO_2R^a groups;

c) Aryl or HAR, each optionally substituted with:

(1) 1-2 C_{1-10}alkyl groups optionally substituted with 1-5 halo groups;

(2) 1-2 C_{1-10}alkoxy groups, the alkyl portion of which is optionally substituted with 1-5 halo groups;

said Aryl or HAR being further optionally substituted on carbon by 1-3 halo groups; up to perhalo;

R^3 is selected from the group consisting of:

a) C_{1-6}alkyl optionally substituted with:

1-3 halo groups up to perhalo;

1 OH, C_{1-3}alkoxy or haloC_{1-3}alkoxy group;

1 NR^cR^d group; and

1 Aryl or HAR group, each optionally substituted with 1-3 halo groups and 1-2 groups selected from C_{1-3}alkyl, haloC_{1-3}alkyl, C_{1-3}alkoxy and haloC_{1-3}alkoxy;

b) Aryl or HAR, each optionally substituted with 1-3 halo groups and 1-2 groups selected from C_{1-3}alkyl, haloC_{1-3}alkyl, C_{1-3}alkoxy and haloC_{1-3}alkoxy;

R^4 represents an Aryl or HAR group, each optionally substituted as set forth below:

(1) 1-2 C_{1-10}alkyl or C_{2-10}alkenyl groups, which are optionally substituted with 1-3 halo groups, or phenyl optionally substituted with 1-2 halo, C_{1-4}alkyl or alkoxy groups, each being further optionally substituted with 1-3 halo groups;

(2) 1-2 C_{1-10}alkoxy or C_{3-10}alkenyloxy groups, which are optionally substituted with 1-3 halo groups, 1-2 OH or $S(O)_pR^d$, and phenyl optionally substituted as follows: 1-3 halo groups up to perhalo; 1-2 C_{1-6}alkyl or alkoxy groups, each being further optionally substituted with 1-3 halo up to perhalo, or 1-2 hydroxy or CO_2R^a groups;

(3) 1-2 Aryl, HAR or Hetcy, OAryl, OHAR or OHetcy groups, each optionally substituted as follows:

(i) 1-3 halo groups;

(ii) 1-2 C_{1-3}alkyl or C_{2-4}alkenyl groups each optionally substituted with 1-3 halo groups, and 1 of OH, phenyl, CO_2R^a, CN and $S(O)_pR^d$;

(iii) 1-2 C_{1-3}alkoxy groups the alkyl portion of which being optionally substituted with 1-3 halo groups, and 1 of OH, phenyl, CO_2R^a, CN and $S(O)_pR^d$; and

(iv) 1-2 CO_2R^a, $S(O)_pR^d$, CN, NR^bR^c, NO_2 or OH groups;

said Aryl, HAR or Hetcy group R^4 being further optionally substituted on carbon by a group selected from the group consisting of;

(4) 1-5 halo groups;

(5) 1-2 OH groups;

(6) 1 $S(O)_pR^d$, NO_2 or CN group;

R^5 represents H or CH_3;

R^8 is selected from the group consisting of H and C_{1-3}alkyl;

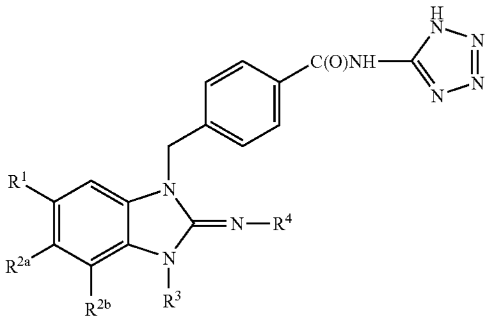
R^6 , R^7 and R^9 represents H;

and m is 0 and n is an integer selected from 0 to 2, such that when n is 1 or 2, Z is selected from CO_2R^a and 5-tetrazolyl, and when both m and n are 0, Z is 5-tetrazolyl.

17. A compound in accordance with claim 16 wherein R^1 is selected from consisting of: H, halo, C1-4alkyl, C1-4alkoxy, said alkyl and alkoxy being optionally with 1-3 halo groups.

18. A compound in accordance with claim 1 selected from Table 1a or 1b below:

TABLE 1a



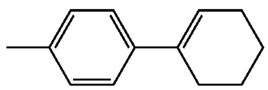
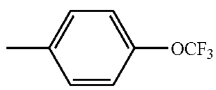
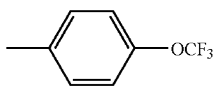
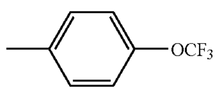
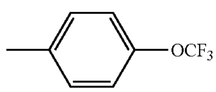
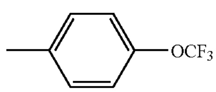
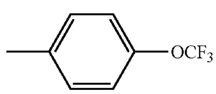
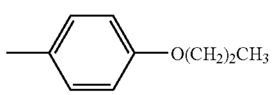
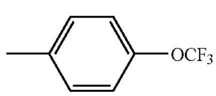
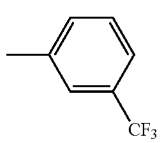
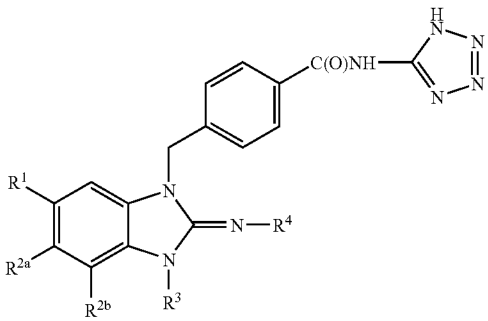
Cpd	R^1	R^{2a}	R^{2b}	R^3	R^4
1	H	H	H	—Me	
2	Cl	Cl	H	—Et	
3	Cl	H	H	—Me	
4	Cl	Cl	H	—Et	
5	—OCF_3	H	H	—Me	
6	Cl	H	—$O(CH_2)_2CH_3$	—Et	
7	—CF_3	Cl	H	—Me	
8	Cl	Cl	H	—Me	
9	Cl	H	Cl	—Me	
10	—CF_3	H	H	—Me	

TABLE 1a-continued



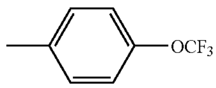
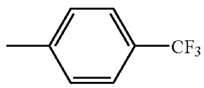
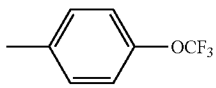
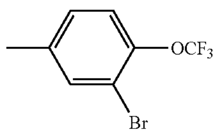
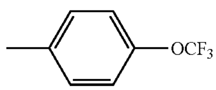
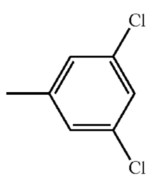
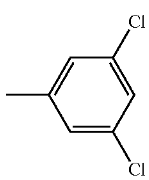
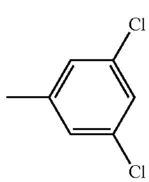
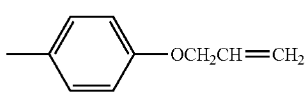
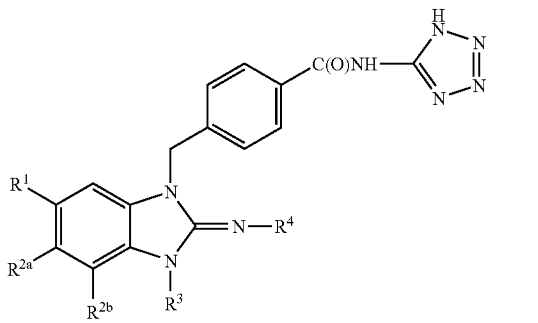
Cpd	R^1	R^{2a}	R^{2b}	R^3	R^4
11	Cl	Cl	H	—Me	
12	—CF_3	H	H	—Me	
13	H	Cl	H	—Me	
14	Cl	Cl	H	—Me	
18	—CF_3	H	H	—Et	
19	H	H	H	—Me	
20	—OMe	H	H	—Me	
22	Cl	Cl	H	—Me	
23	Cl	Cl	H	—Me	

TABLE 1a-continued



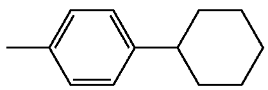
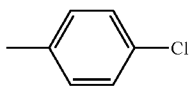
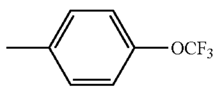
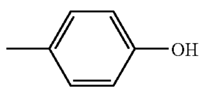
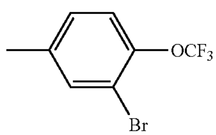
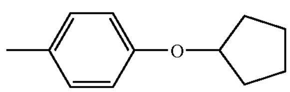
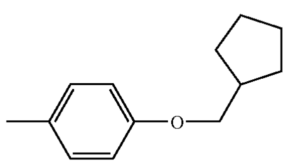
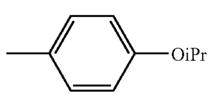
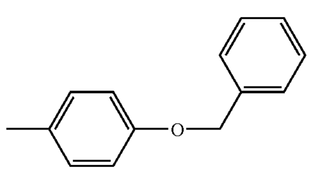
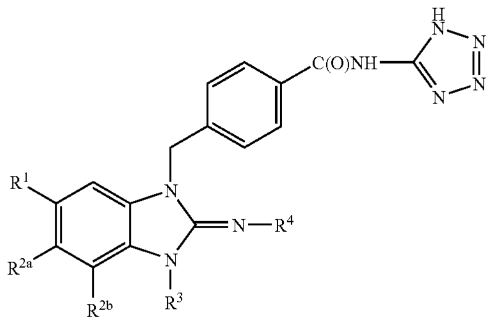
Cpd	R^1	R^{2a}	R^{2b}	R^3	R^4
24	Cl	Cl	H	—Me	
26	—CF_3	H	H	—Me	
27	—OnPr	H	H	—Me	
28	Cl	Cl	H	—Me	
31	Cl	Cl	H	—Et	
32	Cl	Cl	H	—Me	
33	Cl	Cl	H	—Me	
34	Cl	Cl	H	—Me	
35	Cl	Cl	H	—Me	

TABLE 1a-continued



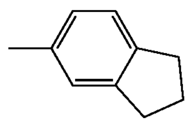
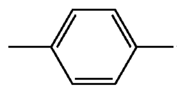
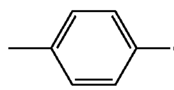
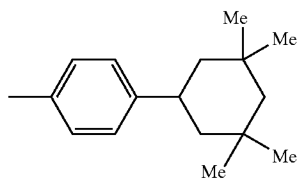
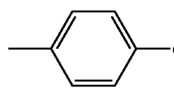
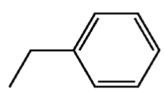
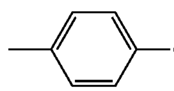
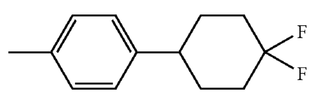
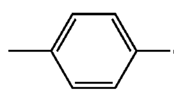
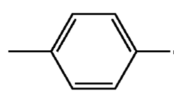
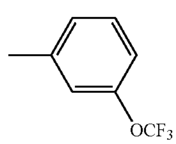
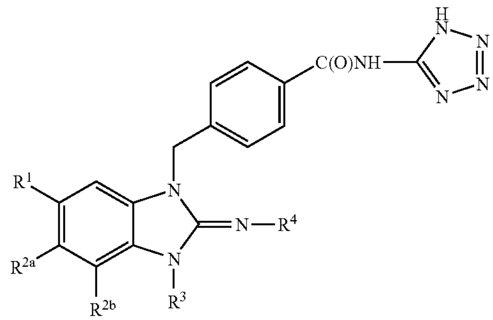
Cpd	R^1	R^{2a}	R^{2b}	R^3	R^4
36	Cl	Cl	H	—Me	
37	Cl	Cl	H	—Me	
38	Cl	Cl	H	—Me	
39	—OMe	H	H	—Me	
40	Cl	Cl	H	—Me	
41	Cl	Cl	H		
42	—OMe	H	H	—Me	
43	Cl	H	—OnBu	—Me	
44	H	—OnPr	H	—Me	
45	Cl	Cl	H	—Me	

TABLE 1a-continued



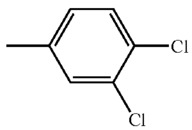
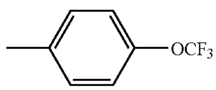
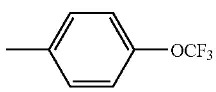
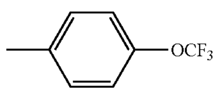
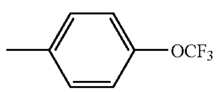
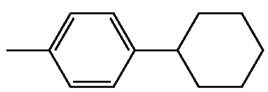
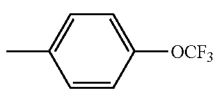
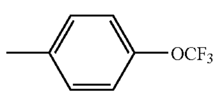
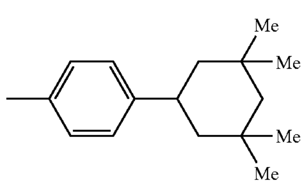
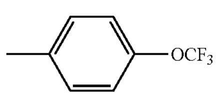
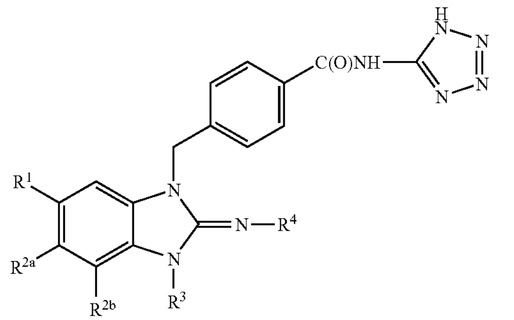
Cpd	R^1	R^{2a}	R^{2b}	R^3	R^4
46	Cl	Cl	H	—Me	
47	Cl	Cl	H	$—CH_2CH_2F$	
48	Cl	Cl	H	iPr	
49	Cl	Cl	H	$—(CH_2)_2OMe$	
50	Cl	Cl	H	$—(CH_2)_2NMe_2$	
51	CF_3	H	H	Me	
52	CF_3	H	CF_3	Me	
53	Cl	Cl	H	$—(CH_2)_3OMe$	
54	CF_3	H	H	Me	
55	CF_3	H	Br	Me	

TABLE 1a-continued



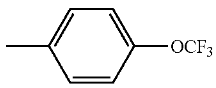
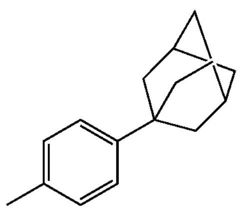
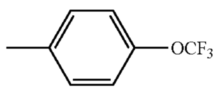
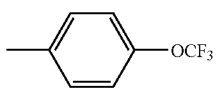
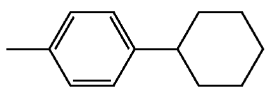
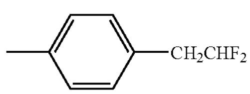
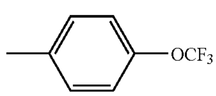
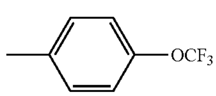
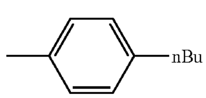
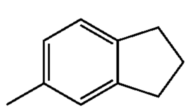
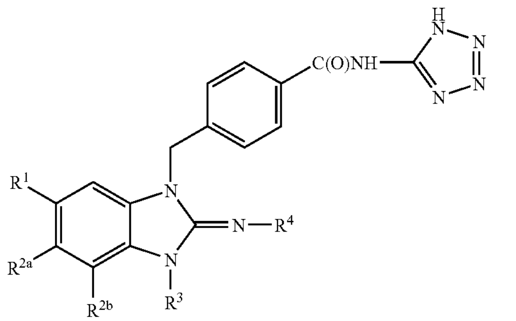
Cpd	R^1	R^{2a}	R^{2b}	R^3	R^4
56	Cl	Cl	H	$—(CH_2)_3NMe_2$	
57	OMe	H	H	Me	
58	Cl	H	OMe	Me	
59	CF_3	H	Et	Me	
60	Cl	H	OMe	Me	
61	H	—OnPr	H	Me	
62	CF_3	H	$—CH{=}CH_2$	Me	
63	CF_3	H	SO_2Me	Me	
64	CF_3	H	H	Me	
65	CF_3	H	Et	Me	

TABLE 1a-continued



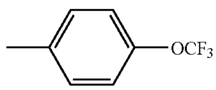
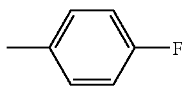
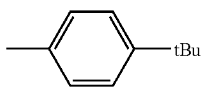
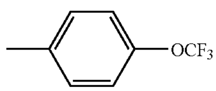
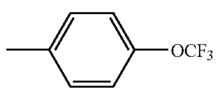
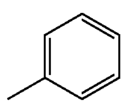
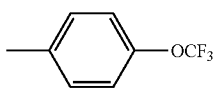
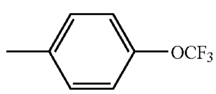
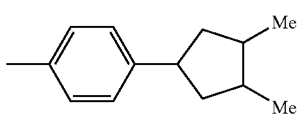
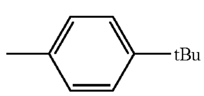
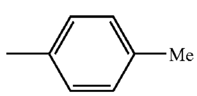
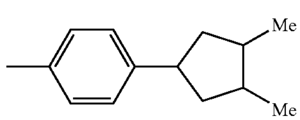
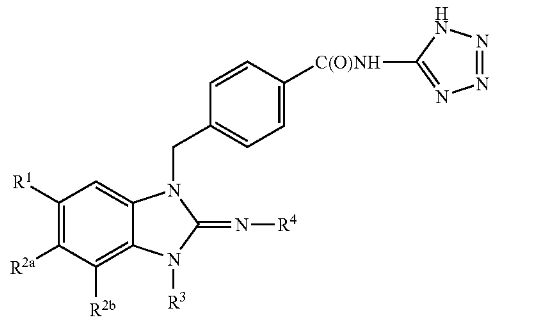
Cpd	R^1	R^{2a}	R^{2b}	R^3	R^4
66	CF_3	H	Me	Me	
67	CF_3	H	Et	Me	
68	CF_3	H	Et	Me	
69	Cl	H	OiPr	Me	
70	Cl	H	OnPr	Me	
71	CF_3	H		Me	
72	Cl	H	OEt	Me	
73	CF_3	H	H	Me	
74	Cl	H	OMe	Me	
75	CF_3	H	Et	Me	
76	OMe	H	H	Me	

TABLE 1a-continued



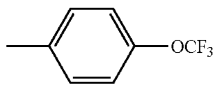
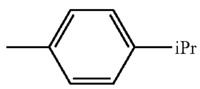
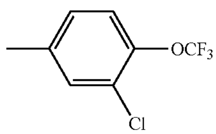
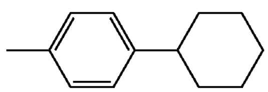
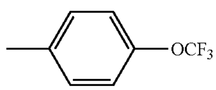
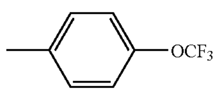
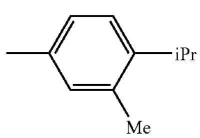
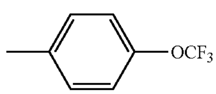
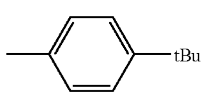
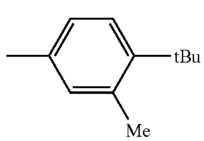
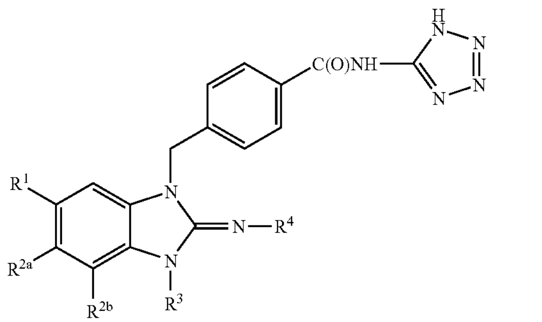
Cpd	R^1	R^{2a}	R^{2b}	R^3	R^4
77	CF_3	H	OnBu	Me	
78	CF_3	H	Et	Me	
79	L	H	OMe	Me	
80	F	H	H	Me	
81	CF_3	H	OMe	Me	
82	Cl	H	OH	Me	
83	OMe	H	H	Me	
84	CF_3	H	OnPr	Me	
85	CF_3	H	OMe	Me	
86	CF_3	H	OMe	Me	

TABLE 1a-continued



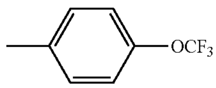
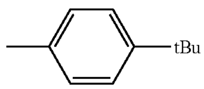
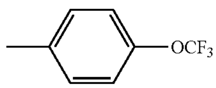
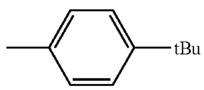
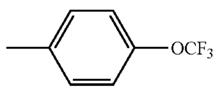
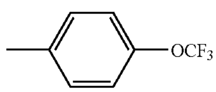
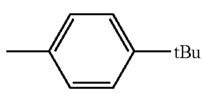
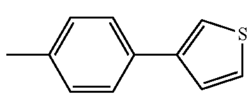
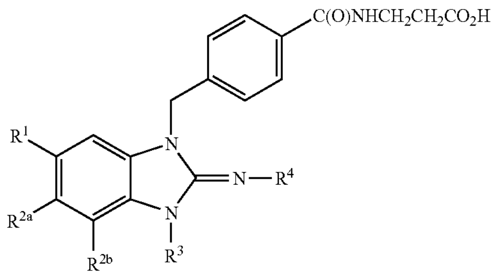
Cpd	R^1	R^{2a}	R^{2b}	R^3	R^4
87	H	H	OnPr	Me	
88	CF_3	H	OnPr	Me	
90	CF_3	H	OEt	Me	
91	CF_3	H	Et	Et	
92	CF_3	H	Et	Et	
95	CF_3	H	Cl	Me	
96	CF_3	H	H	Me	
97	H	OnPr	H	Me	

TABLE 1b



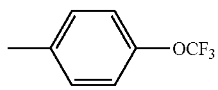
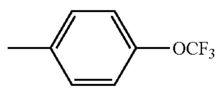
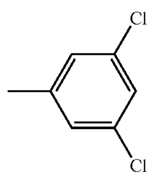
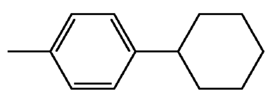
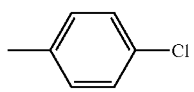
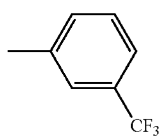
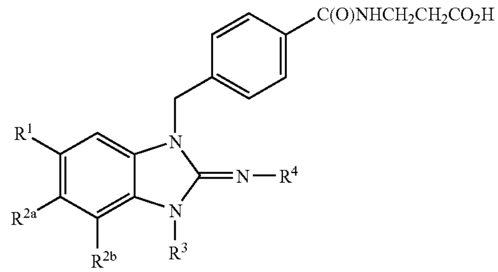
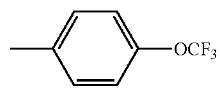
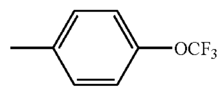
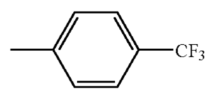
Cpd	R^1	R^{2a}	R^{2b}	R^3	R^4
15	H	Cl	H	Me	
17	Cl	Cl	H	Me	
21	OMe	H	H	Me	
25	Cl	Cl	H	Me	
29	CF_3	H	H	Me	
30	CF_3	H	H	Me	

TABLE 1b-continued



Cpd	R^1	R^{2a}	R^{2b}	R^3	R^4
89	Cl	H	OnPr	Et	
93	H	H	OnPr	Me	
94	CF_3	H	H	Me	

or a pharmaceutically acceptable salt or solvate thereof.

19. A pharmaceutical composition comprising a compound in accordance with claim 1 in combination with a pharmaceutically acceptable carrier.

20. A method of treating type 2 diabetes mellitus in a mammalian patient in need of such treatment comprising administering to said patient a compound in accordance with claim 1 in amount that is effective to treat said type 2 diabetes mellitus

21-44. (canceled)

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